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Studies on the Total Synthesis of (±)-Rocaglamide

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Studies on the Total Synthesis of (±)-Rocaglamide

by

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Dedication

To my wife, Amy, who gave me the support I needed to succeed and whose patience with me throughout graduate school has helped me to pursue my dreams.

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I would like to thank Professor Philip Magnus for all of his wisdom, guidance, and support throughout my graduate career. I am also in debt to all of the Magnus group members throughout the years, especially Dr. Trevor Rainey for the helpful discussions and work on this project, Dr. Evan Hecker for the many thought-provoking discussions, and Mr. Neeraj Sane who has been of great help. I would also like to thank Vince Lynch for all of the help with X-ray crystallography and structural elucidation.

Studies on the Total Synthesis of (±)-Rocaglamide

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Supervisor: Philip D. Magnus

The use of a Nazarov cyclization for the diastereoselective synthesis of rocaglamide was studied. Chapter 1 discusses the biological activity of the rocaglamide family of natural products and details the previous synthetic work on these compounds. Chapter 2 discusses the approaches taken in the Magnus group for the total synthesis of rocaglamide. Several approaches to the natural product were undertaken. Using a novel acid bromide induced Nazarov cyclization, construction of the C-ring of the natural product was achieved. Attempts to construct the remainder of rocaglamide were ultimately unsuccessful.

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List of Abbreviations

1,2-DCE	1,2-dichloroethane
Å	ångstrom
Ac	acetyl
AcBr	acetyl bromide
An	anisyl
Atm	atmosphere
Bz	benzoyl
BzBr	benzoyl bromide
CAN	ammonium cerium (IV) nitrate
cat.	catalytic
m-CPBA	*m*-chloroperoxybenzoic acid
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dd	doublet of doublets
DIBAL-H	diisobutylaluminum hydride
dioxane	1,4-dioxane
DIPEA	diisopropylethylamine (Hünig's base)
DMDO	dimethyldioxirane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMF	N,N-dimethylformamide
equiv.	equivalents
EtOAc	ethyl acetate
g	gram
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HRMS	high-resolution mass spectrometry
IR	infrared spectrometry
LDA	lithium diisopropylamide
m	multiplet
m	meta
M	molar
Me	methyl

mg	milligram
mL	milliliter
mmol	millimole
mol	mole
M.p	melting point
NBS	N-bromosuccinimide
ng	nanogram
nm	nanometer
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
ppm	parts per million
p-TsCl	*para*-toluenesulfonyl chloride
Py·BOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
pyr.	pyridine
q	quartet
R	alkyl
s	singlet
t	triplet
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	trimethylsilyl
TPP	5,10,15,20-tetraphenylporphyrin

Chapter 1: Introduction to the Rocaglamide Family of Natural Products

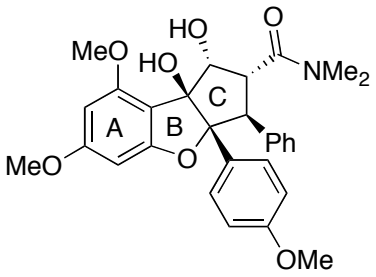
1.1 Introduction

The genus *Aglaia*, which consists of approximately 130 species of plants found in the Indo-Malaysian region, South China and on the Pacific Islands, is the source of a unique group of natural products consisting of a cyclopenta[*b*]tetrahydrobenzofuran skeleton. These compounds are commonly known as the rocaglamides. Their name was taken from the parent compound, rocaglamide, which was first isolated in 1982. The rocaglamides have received much attention because of their remarkable biological activity in the areas of insecticides and anti-cancer agents. The flowers of *A. odorata* have traditionally been used in folk medicine as a heart stimulant, febrifuge, and for the treatment of coughs, inflammations and injuries. They have additionally been used as insect repellent in parts of South East Asia and to protect clothes from moths in Vietnam.[1]

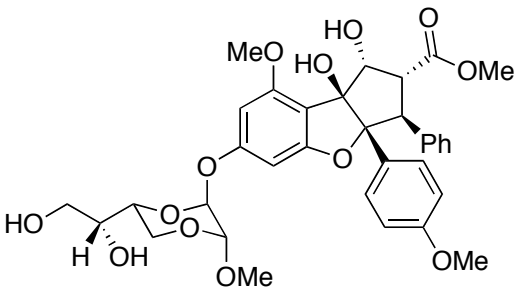
1.2 Isolation and Biological Activity

Rocaglamide **1.2.1** was isolated from the dried stems and roots of *Aglaia elliptifolia* Merr. (Meliaceae) in 1982 by King *et. al.* and its structure was determined by X-ray crystallography.[2] It was reported to exhibit significant antileukemic activity against P388 lymphocytic leukemia in CDF_1 mice and inhibitory activity *in vitro* against cells derived from human epidermoid carcinoma of the nasopharynx (KB cell). Since

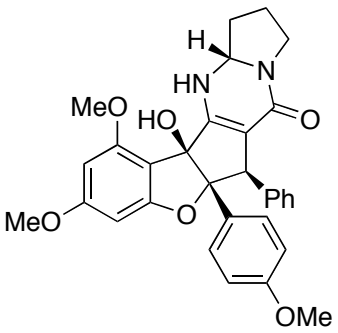
then, more than 50 different rocaglamide congeners have been isolated from *Aglaia* spp (Figure 1.2.1).[1]



Rocaglamide 1.2.1



Silvestrol 1.2.2



Aglaiastatin 1.2.3

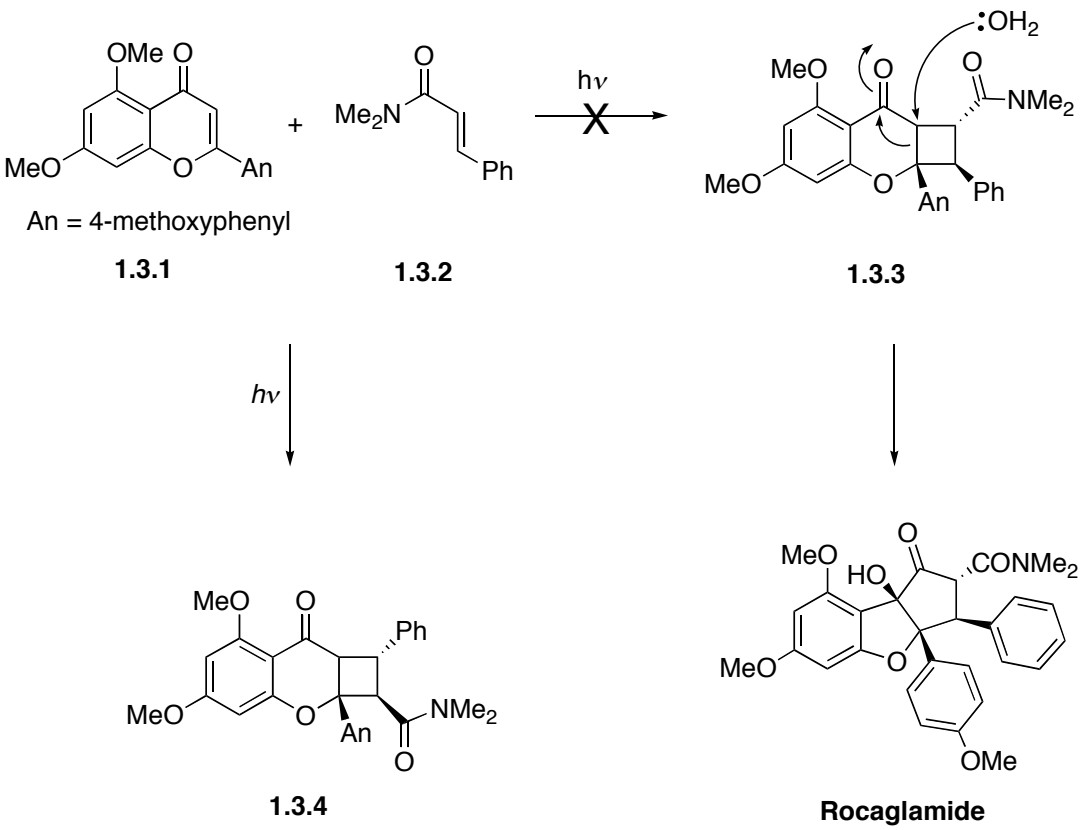
Figure 1.2.1 Representative members of the rocaglamide family

The rocaglamide family has shown a broad range of biological activities. Almost all naturally occurring rocaglamide members display potent insecticidal activity, with the activity of the most potent being comparable to that of azadirachtin.[3] More importantly these compounds have exhibited very good anti-tumor activity.[1,4-7] The inhibition of numerous human cancer cell lines has been shown including A-549 (human lung carcinoma), RPMI-7951 (human melanoma), TE-671 (human rhabdomyosarcoma) and

KB cells (human cervix carcinoma) with IC_{50} values ranging from 1.0 - 6.0 ng/mL.[8] Rocaglamide itself has been shown to operate through a cytostatic mechanism at low concentrations (1-10 ng/mL)[9], while triggering apoptosis in leukemia cells at higher concentrations (25 ng/mL).[10] The rocaglamides also function as inhibitors of NF-κB activation in T-cells[11] and as immunosuppressive phytochemicals targeting NF-AT activity in T-cells.[12] While the compounds are potent anti-tumor agents, they show low toxicity toward normal cells. All of this data makes the rocaglamides interesting candidates for therapeutic agents in the field of cancer.

1.3 Proposed Biosynthetic Pathways to the Rocaglamides

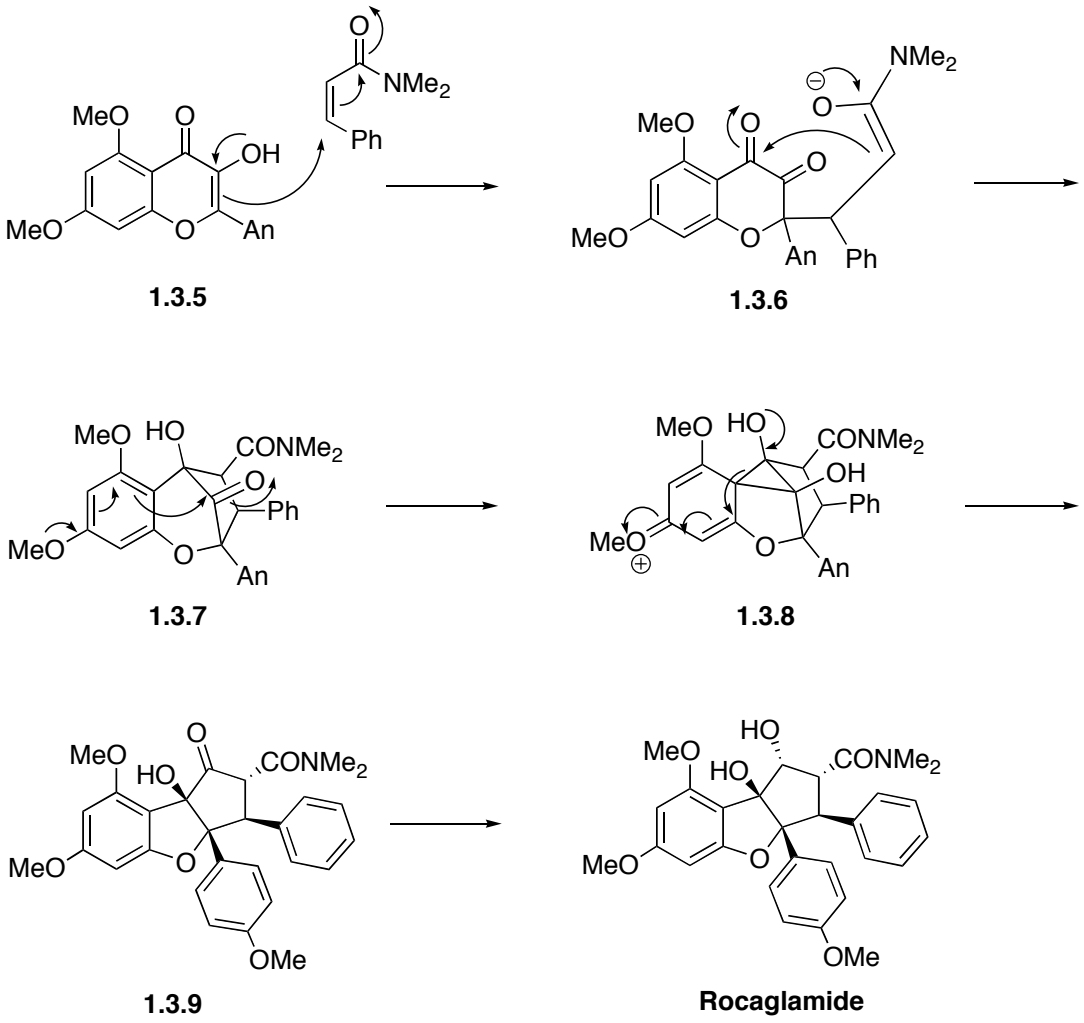
Staunton proposed the first biosynthetic route to the rocaglamides in 1993.[13] He proposed that the tricyclic core could arise from a photochemically induced [2+2] cycloaddition of flavone **1.3.1** and a cinnamate unit **1.3.2** to form a bicyclo [6,4] ring system. This system could then undergo a rearrangement to the [5,5] system (Scheme 1.3.1). Experimentally, however, he found that the [2+2] cycloaddition gave exclusively the wrong regiochemistry **1.3.4**. Porco would later prove in his biomimetic synthesis of rocaglamide that a [2+2] cycloaddition is plausible starting from a 3-hydroxyflavone.[17]



Scheme 1.3.1 Staunton's Biomimetic Approach

Proksch *et. al.*[1] proposed their own hypothesis for the biogenetic origin of the rocaglamide skeleton (Scheme 1.3.2). They reasoned that 3-hydroxyflavone **1.3.5** could perform a Michael-type addition to a cinnamide moiety to generate **1.3.6**. The resulting amide enolate could then attack at the C-4 carbon of the starting flavonoid to generate the five-membered ring of **1.3.7**. They proposed that migration of the phloroglucinol-derived aromatic ring could occur *via* electrophilic aromatic *ipso*-substitution to form the intermediate **1.3.8**. Opening of the cyclopropane could restore the aromaticity of the A-

ring yielding cyclopentanone **1.3.9**. Reduction of the ketone with a hydride source such as NADPH would give rocaglamide.



Scheme 1.3.2 Proksch's Biosynthetic Proposal

Interestingly, the conjugate addition in nature is neither regioselective nor stereoselective since all four stereoisomers exist. This information is important to note when designing a synthesis toward rocaglamide, since one based on a biosynthetic route

would most likely require the separation of multiple compounds along the synthetic route.

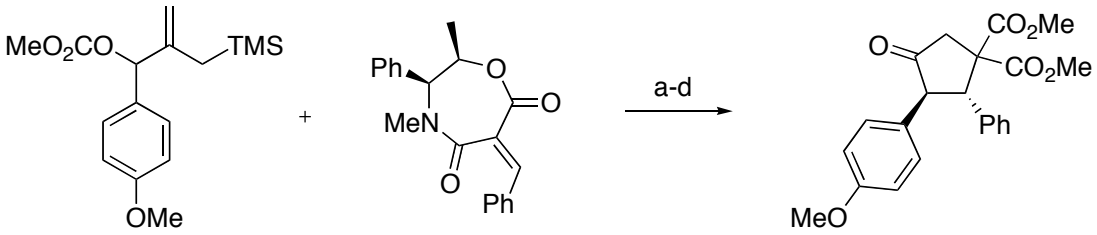
1.4 Previous Studies on the Rocaglamides

The rocaglamides have attracted the attention of many investigators because of their interesting structures and significant biological activities. To date, total syntheses of rocaglamide have been reported by Trost,[14] Taylor,[15] a process group at Novartis,[16] Porco[17-19] and Frontier.[33] The Trost and Porco routes are enantioselective, while the syntheses by Taylor, Novartis and Frontier are racemic.

Syntheses of other members of the rocaglamide family have also been reported. Aglaiastatin has been synthesized using Taylor's approach to the core.[20] Porco[21] and Rizzacasa[22,23] have both achieved total syntheses of silverstrol employing Porco's [3+2] cycloaddition strategy. There have also been numerous efforts involving various strategies toward the tricyclic core of the rocaglamides.[24-31]

1.4.1 Trost's Enantioselective Synthesis

The first total synthesis of rocaglamide was reported by the Trost group in 1990 (Scheme 1.4.1).[14] The synthesis began with a palladium-catalyzed cycloaddition of trimethylenemethane precursor **1.4.1** and oxazepinedione **1.4.2**. Subsequent hydrolysis of the auxiliary, esterification, and ozononlysis gave the optically pure cyclopentanone **1.4.3**.

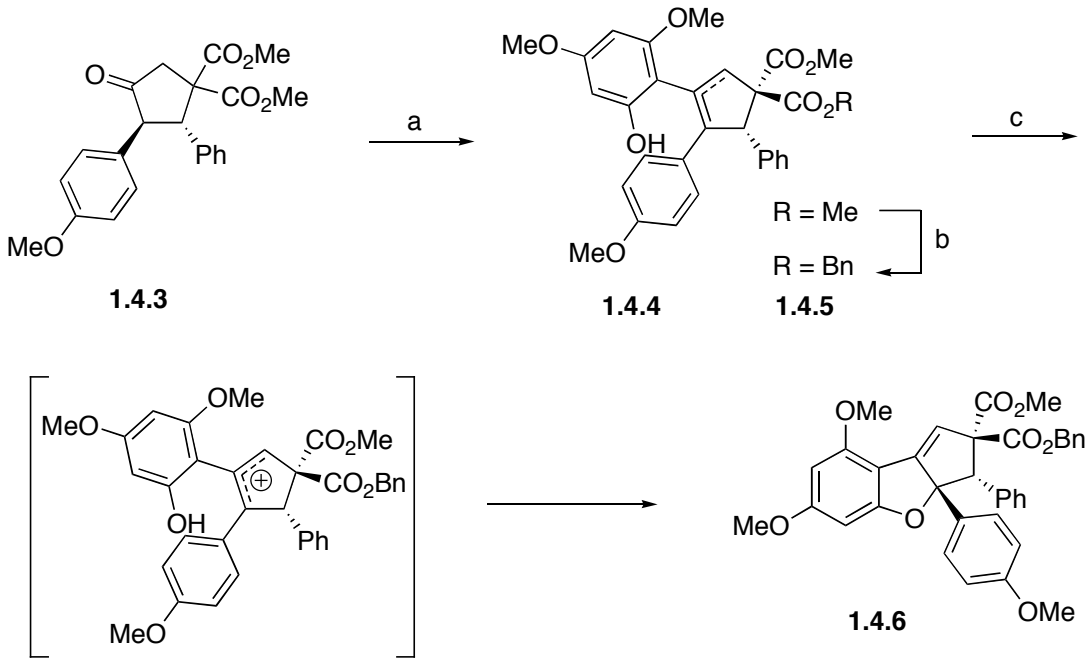


1.4.1 **1.4.2** **1.4.3**

Conditions: (a) $Pd(OAc)_2$, P^iPr_3, toluene; (b) NaOH, EtOH; (c) CH_2N_2, EtOAc; (d) O_3, MeOH, CH_2Cl_2 then DMS, 85% (4 steps);

Scheme 1.4.1 Formation of the C-ring

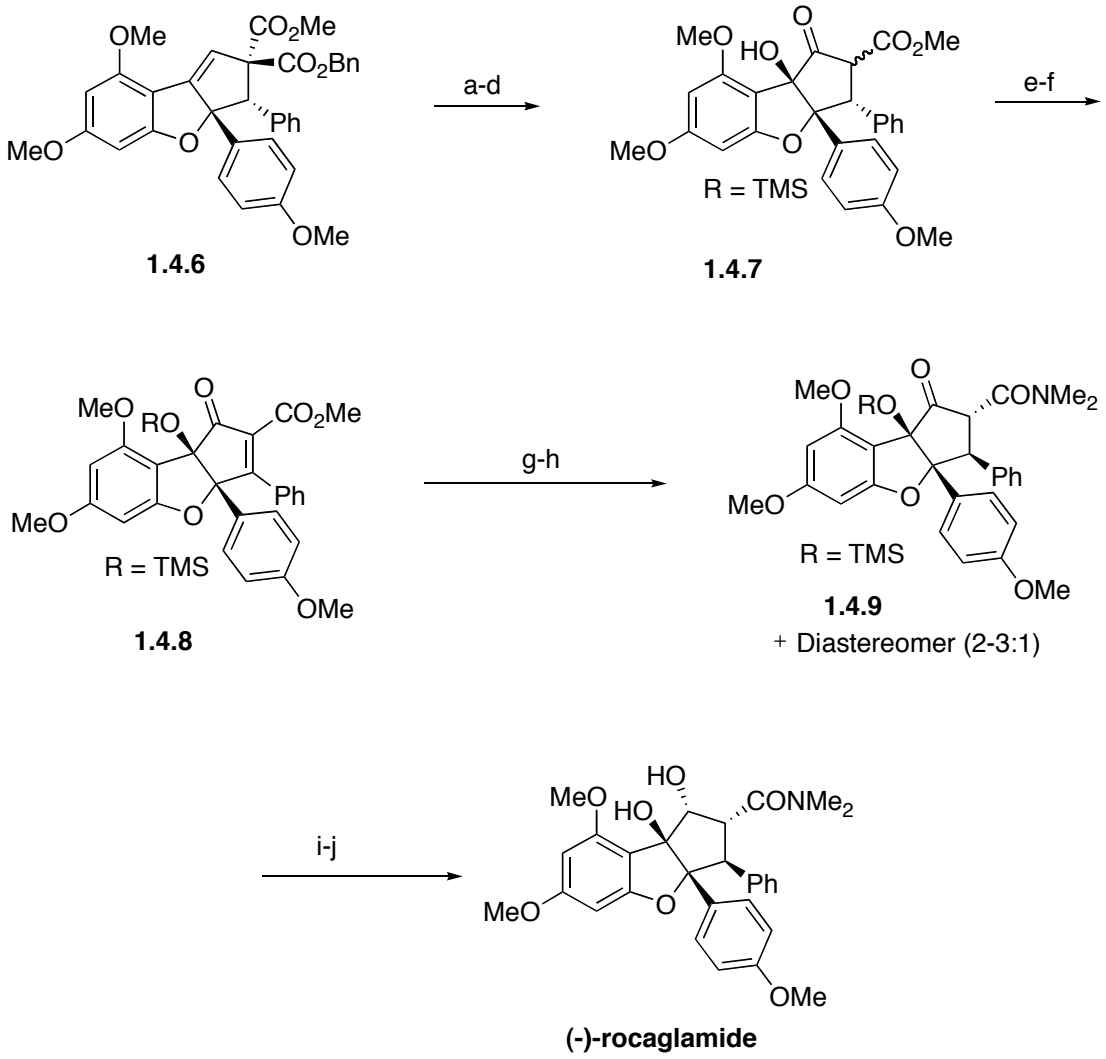
The condensation of 3,5-dimethoxyphenol and **1.4.3** with a BF_3•CH_3OH complex gave **1.4.4** as a 2:1 mixture of olefin regioisomers (Scheme 1.4.2). Transesterification of one methyl ester with benzyl alcohol produced **1.4.5**. Oxidative cyclization of **1.4.5** using DDQ occurred *via* an allylic cation, where the phenolic oxygen attacked at the position of highest positive charge, to form the tricyclic core **1.4.6**. Surprisingly, the approach of the phenolic oxygen occurred on the same face as the phenyl substituent. This was contrary to Trost's prediction that the attack would come from the least hindered face, opposite the phenyl. This result meant that additional steps were needed to invert the phenyl stereochemistry and obtain a *cis* relationship between the phenyl and anisyl substituents.



Conditions: (a) 3,5-dimethoxyphenol, BF_3·MeOH, CH_2Cl_2, 60%; (b) $Ti(OBn)_4$, BnOH, 78%; (c) DDQ, THF, 75%

Scheme 1.4.2 Formation of the tricyclic core

Dihydroxylation of **1.4.6** and oxidation to the ketone, followed immediately by silylation and decarbobenzyloxylation gave the keto ester **1.4.7** in 60% overall yield (Scheme 1.4.3). To invert the C-3 stereochemistry, the enone was first installed by sulfenylation/dehydrosulfenylation to yield **1.4.8**. Amidation using Weinreb's conditions followed by reduction of the enone with Pearlman's catalyst resulted in a 2-3:1 mixture of diastereomers (**1.4.9**) favoring the *cis* orientation of the two aryl substituents. Desilylation followed by templated reduction with $(CH_3)_4NB(OAc)_3H$ furnished (-)-rocaglamide.



Conditions: (a) OsO_4, NMO, DABCO, THF, H_2O, 73%; (b) SO_3·pyridine, Et_3N, DMSO; (c) TMSOTf, $^{i}Pr_2NEt$, benzene; (d) H_2, 10% Pd/C, EtOH, 60% (3 steps); (e) NaH, PhSCl, THF; (f) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 72% (2 steps); (g) Me_2NH_2Cl, Me_3Al, benzene, 70-79%; (h) H_2, 20% $Pd(OH)_2$/C, EtOH; (i) KF, MeOH; (j) $Me_4NB(OAc)_3H$, MeCN, AcOH, 50% (3 steps).

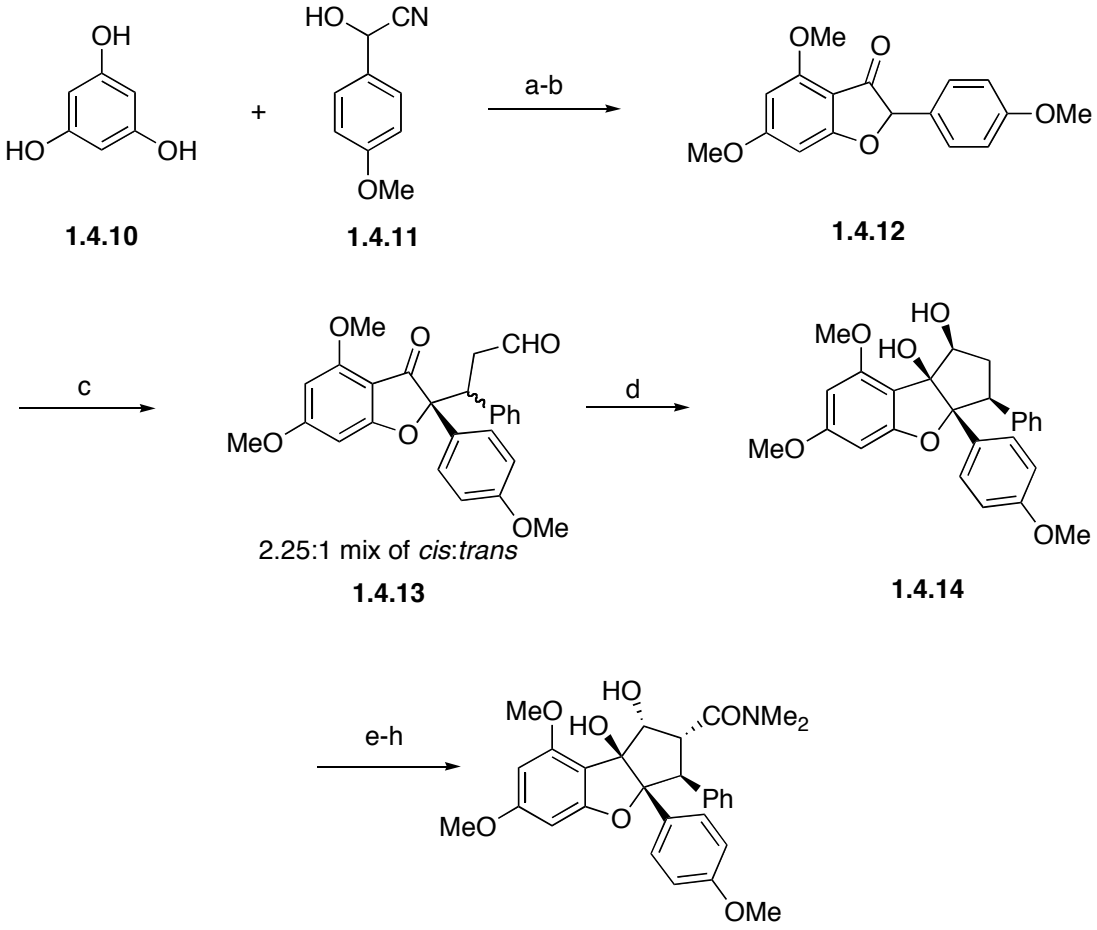
Scheme 1.4.3 Inversion of phenyl stereochemistry and completion of synthesis

Trost's synthesis was important because it established the absolute stereochemistry of (-)-rocaglamide. It also showed the unique steric congestion present in the oxidative ring closure, and that a templated reduction can achieve the desired *trans*

diol present in the natural product. However, his synthesis suffered due to its length, as well as, a "problematic" hydrogenation of the enone to obtain the required *cis* stereochemistry of the aryl groups.

1.4.2 Taylor's Route to Rocaglamide

Taylor's approach to rocaglamide is based upon a conjugate addition of benzofuranone **1.4.12** to (E)-cinnamaldehyde followed by a pinacolic coupling to give the tricyclic core of rocaglamide.[15] The synthesis began with a Houben-Hoesch reaction between phloroglucinol **1.4.10** and cyanohydrin **1.4.11**. Methylation of the phenolic oxygens with dimethyl sulfate and potassium carbonate provided benzofuranone **1.4.12** (Scheme 1.4.4). Conjugate addition of the benzofuranone to cinnamaldehyde using Triton B® gave at best a 2.25:1 mixture of diastereomers **1.4.13**, with the required *cis* configuration predominating. The pinacolic coupling occurred upon treatment of the keto-aldehyde with SmI_2 to yield **1.4.14**. The yields of this reaction, however, were found to be highly irreproducible, with yields ranging from 45-60%. Oxidation of the secondary alcohol, followed by amide formation and selective reduction to the *trans* diol, completed the synthesis.



Conditions: (a) HCl (g), Et_2O, then aq. HCl, 50-76%; (b) Me_2SO_4, K_2CO_3, acetone, then aq. HCl, 91%; (c) *E*-cinnamaldehyde,Triton B, ^tBuOH, 69%; (d) SmI_2, THF, 58%; (e) $(COCl)_2$, DMSO, Et_3N, THF, 81%; (f) (i)TMSOTf, DIPEA, toluene (ii) LDA, HMPA, CS_2, then MeI (iii) MeONa, THF, 55% overall; (g) Me_2NLi,THF, 89%; (h) $Me_4NBH(OAc)_3$, AcOH-MeCN, 81%.

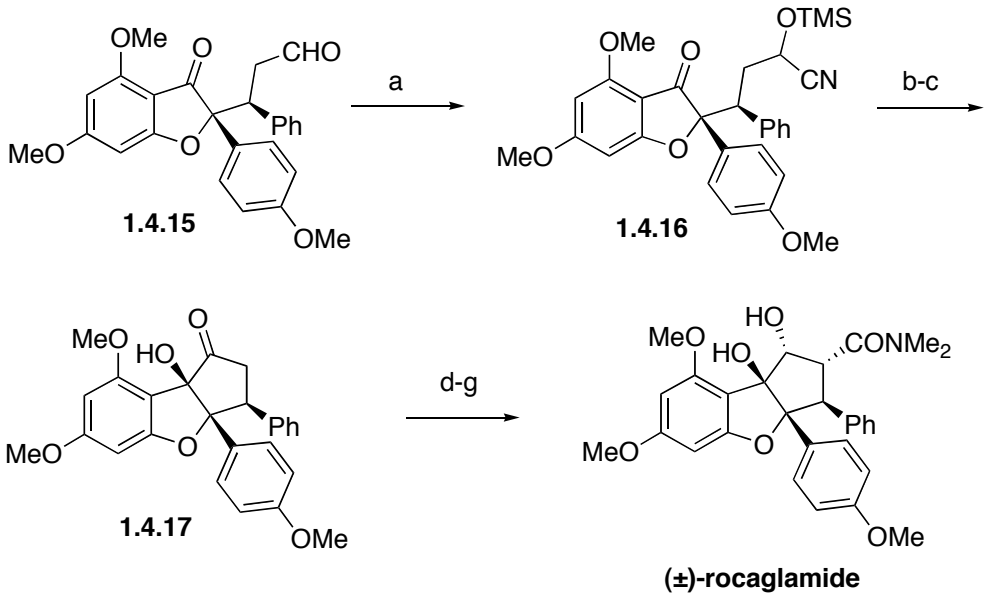
Scheme 1.4.4 Taylor's total synthesis of (±)-rocaglamide

Although Taylor's synthesis was much shorter than Trost's, it still left some room for improvement. The conjugate addition gave a mixture of diastereomers that required separation to get the stereochemistry required in the natural product. In addition, the

SmI_2 promoted pinacolic coupling was not reproducible and most likely would not be very amenable to a large-scale synthesis.

1.4.3 Novartis' Variation on Taylor's Route

A Novartis process group wanted to avoid the pinacolic coupling that Taylor had used because of the poor yields and low reproducibility. A variation of Taylor's synthesis was envisioned that would allow for an anionic closure of the C-ring (Scheme 1.4.5).[16] After using Taylor's method to obtain keto-aldehyde **1.4.15**, TMS-protected cyanohydrin **1.4.16** was formed by treatment with TMSCN and ZnI_2. Deprotonation of this compound with LDA caused the cyclization to form the C-ring. Deprotection of the cyanohydrin with potassium carbonate then gave **1.4.17**. To install the amide moiety, the cyclopentanone was treated with Stiles' reagent followed by hydrolysis of the methyl ester and amide coupling with dimethylamine. Selective reduction with tetramethylammonium triacetoxyborohydride, as previously reported, gave the final target.



Conditions: (a) TMSCN, ZnI_2, CH_3CN/benzene, quant.; (b) LDA, THF; (c) K_2CO_3, MeOH, 73% (2 steps);(d) $MeOMgOCO_2Me$, DMF; (e) 6N HCl; (f) $HNMe_2$, Py·BOP, CH_2Cl_2, 70% (3 steps); (g) $Me_4NBH(OAc)_3$,MeCN, AcOH, 95%.

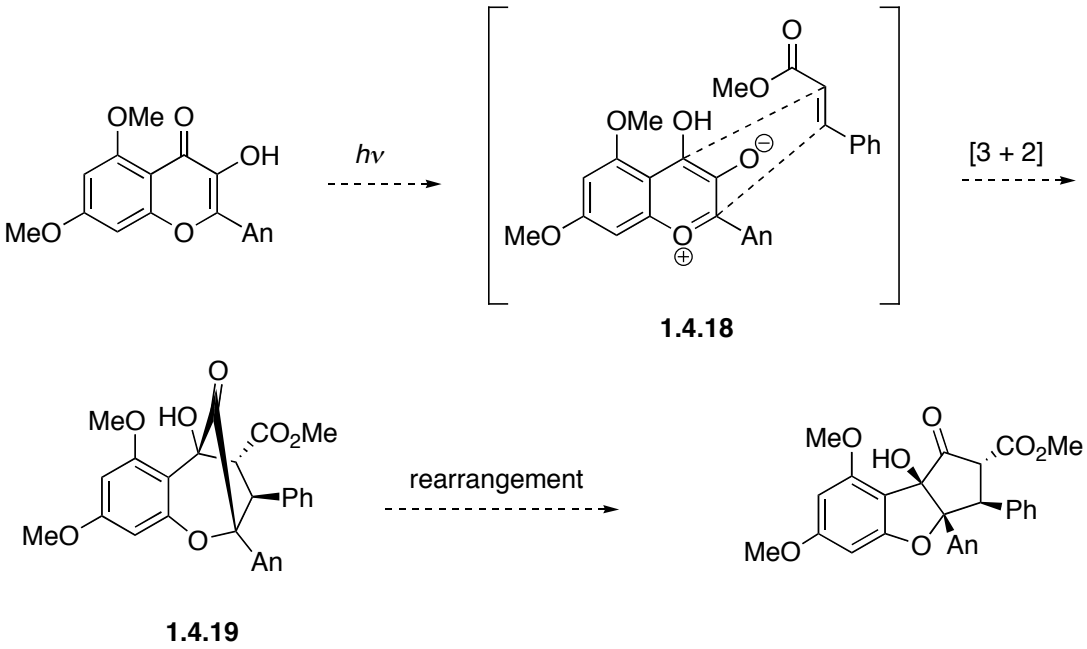
Scheme 1.4.5 Novartis' variation on Taylor's approach

Although the Novartis strategy avoided the use of SmI_2 to form the tricyclic core, the issue of diastereoselectivity in relation to the two aryl substituents had not been addressed.

1.4.4 Porco's [3+2] Strategy

Porco's synthesis was based on the proposed biosynthesis by Proksch.[17] It was believed that exposure of a 3-hydroxyflavone to UV light would form oxidopyryllium species **1.4.18** that could undergo a [3+2] cycloaddition with a cinnamic acid derivative

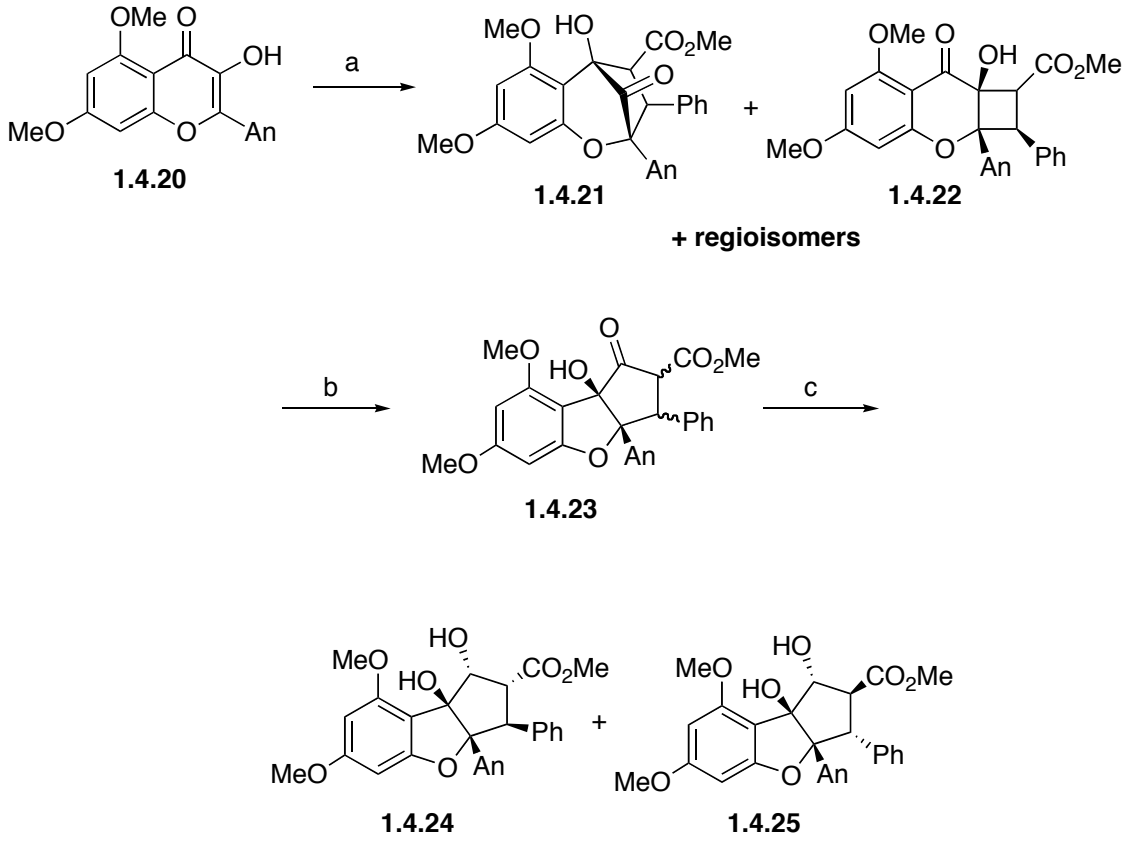
to give the aglain core **1.4.19**. This could then be converted to the rocaglamide core *via* acyloin rearrangement (Scheme 1.4.6).



Scheme 1.4.6 Proposed synthetic route

The synthesis began with 3-hydroxyflavone **1.4.20**, which is obtained by a five step sequence starting from 3,5-dimethoxyphenol.[18] Photoirradiation (uranium filter) with a 450 W medium-pressure mercury lamp in the presence of methyl cinnamate in methanol gave a mixture of aglain **1.4.21** in 33% yield and benzo[*b*]cyclobutapyran-8-one **1.4.22** in 17% yield (Scheme 1.4.7). It should be noted that products containing the opposite regiochemistry from the [3+2] and the [2+2] cycloadditions were also obtained. After separation of the regioisomers, the mixture of **1.4.21** and **1.4.22** was treated with sodium methoxide in methanol to induce the α-ketol rearrangement to **1.4.23**, which was obtained as a mixture of compounds in 95% yield. The two compounds were reduced to

the *trans* diols yielding methyl rocaglate **1.4.24** in 51% yield and **1.4.25** in 17% yield. Methyl rocaglate **1.4.24** could be converted to rocaglamide *via* saponification followed by amide coupling.



Conditions: (a) methyl cinnamate, *hν* (350 nm), MeOH, **1.4.21** (33%) **1.4.22** (17%); (b) NaOMe, MeOH, 95%; (c) $Me_4NBH(OAc)_3$,MeCN, AcOH, **1.4.24** (51%) **1.4.25** (27%).

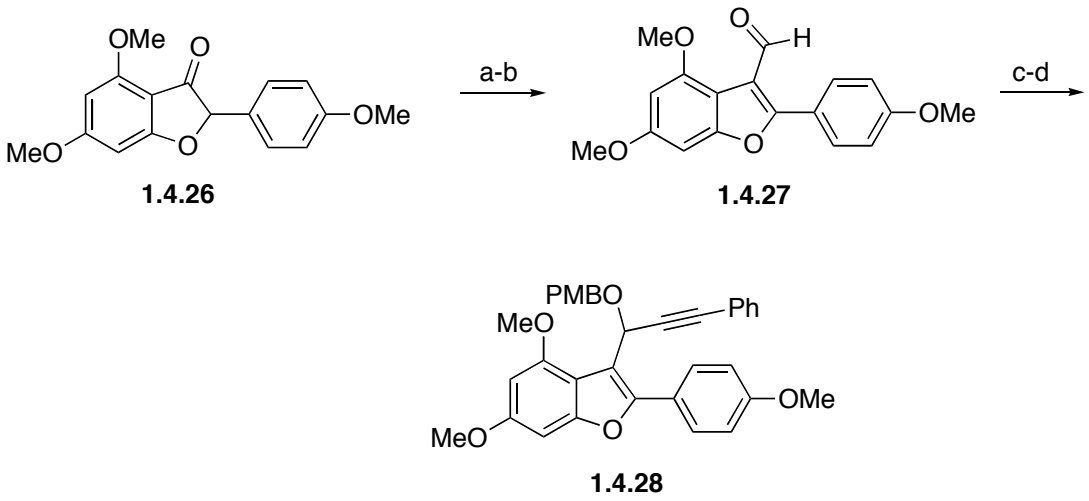
Scheme 1.4.7 Porco's synthesis of the rocaglamide core

Although Porco's synthesis is the shortest to the rocaglamides, it suffers from the fact that the photocyclization is neither regio- nor stereoselective, thus requiring the separation of multiple products at two stages along the synthetic route. This result is not

surprising considering all of the stereoisomers are known to exist in nature, and his synthesis is based on the biosynthetic proposal. Porco later published an enantioselective route using chiral Brϕnsted acids as mediators in the [3+2] photocyclization.[19]

1.4.5 Frontier's Total Synthesis of Rocaglamide

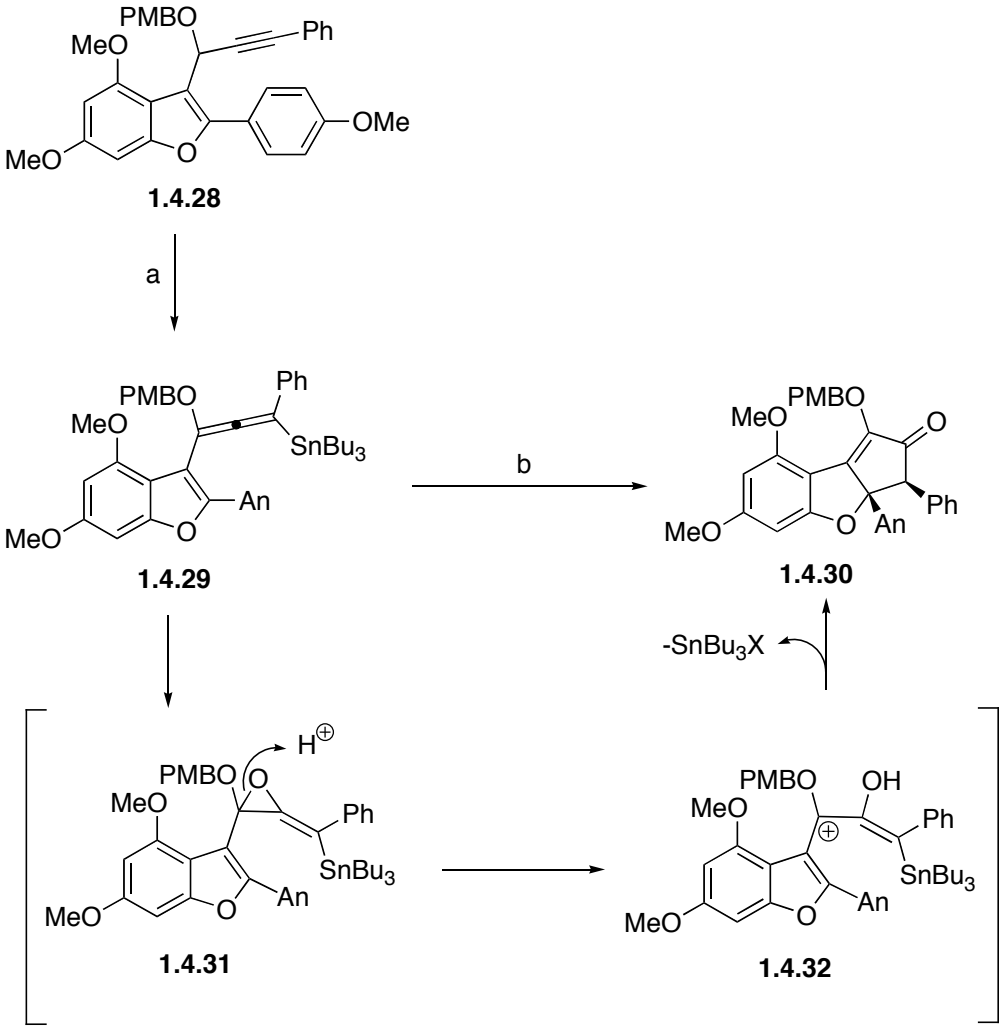
The Frontier group recently reported the total synthesis of (±)-rocaglamide based on a novel Nazarov cyclization to form the C-ring.[33] Their synthesis began with benzofuranone **1.4.26**, which was available through a three step sequence laid out by Taylor.[15] Treatment of the benzofuranone with vinyl magnesium bromide, followed by dihydroxylation and periodate cleavage gave aldehyde **1.4.27** (Scheme 1.4.8). Addition of lithiated phenylacetylene to the aldehyde and treatment of the resultant propargylic alcohol with *p*-methoxybenzyl chloride provided propargylic ether **1.4.28**.



Conditions: (a) $CeCl_3$, vinyl magnesium bromide, then 1M HCl, 65%; (b) (i) OsO_4 (4 mol%), NMO, acetone/*t*-BuOH/H_2O, (ii) $NaIO_4$, THF/H_2O; (c) phenylacetylene, *n*-BuLi, THF; (d) KH, NaI, PMBCl, THF, 69% (over 3 steps)

Scheme 1.4.8 Formation of propargylic ether

Treatment of **1.4.28** with *t*ert-butyllithium and trapping of the allenyl anion with tri-*n*-butyltin chloride gave the stannyl alkoxyallene **1.4.29**, which was set up for a Nazarov cyclization (Scheme 1.4.9). Upon treatment with excess *m*-CPBA, cyclopentenone **1.4.30** was formed as a single diastereomer. The reaction was presumed to proceed *via* epoxidation of the allenyl ether to give **1.4.31**, followed by opening of the epoxide under acidic conditions to pentadienyl cation **1.4.32**, which cyclized to **1.4.30** with loss of the tributylstannyl group.

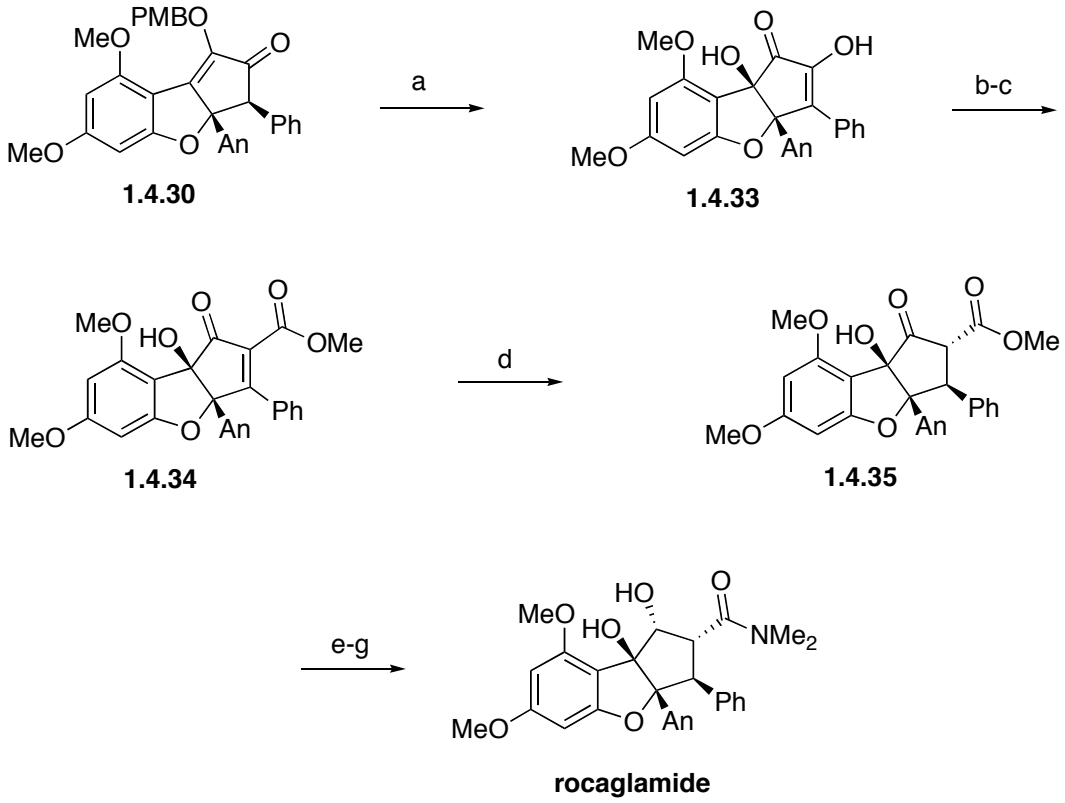


Conditions: (a) *t*-BuLi, Bu_3SnCl, Et_2O; (b) *m*-CPBA, DMF, < 40% (over 2 steps).

Scheme 1.4.9 Peracid initiated Nazarov cyclization

Treatment of **1.4.30** with excess DDQ resulted in the cleavage of the PMB group and oxidation of the benzylic position to give **1.4.33** (Scheme 1.4.10). To introduce the carbonyl moiety at the C-2 position, the enol triflate was formed and subjected to palladium catalyzed carbonylation conditions to yield methyl ester **1.4.34**. Hydrogenation using Trost's conditions[14] furnished cyclopentanone **1.4.35** as a single

diastereomer. Templated reduction, saponification and amide formation completed the synthesis of (±)-rocaglamide.



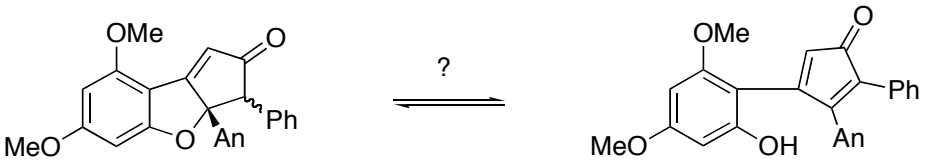
Conditions: (a) DDQ, CH_2Cl_2/H_2O, 71%; (b) KHMDS, $PhNTf_2$, THF, 83%; (c) $Pd(PPh_3)_4$, CO, MeOH, $^iPr_2EtN$, THF, 83%; (d) PtO_2, H_2, EtOH, 65%; (e) $NaHB(OAc)_3$, MeCN/AcOH, 56%; (f) LiOH, THF/H_2O, 82%; (g) $Me_2NH{\cdot}HCl$, DCC, DMAP, 60%.

Scheme 1.4.10 Completion of (±)-rocaglamide

Frontier's synthesis was interesting as it addressed the issues that were encountered during previous work in the Magnus group.[32] The use of an epoxide-opening initiated Nazarov cyclization made this work novel.

1.5 Previous Work in the Magnus Group

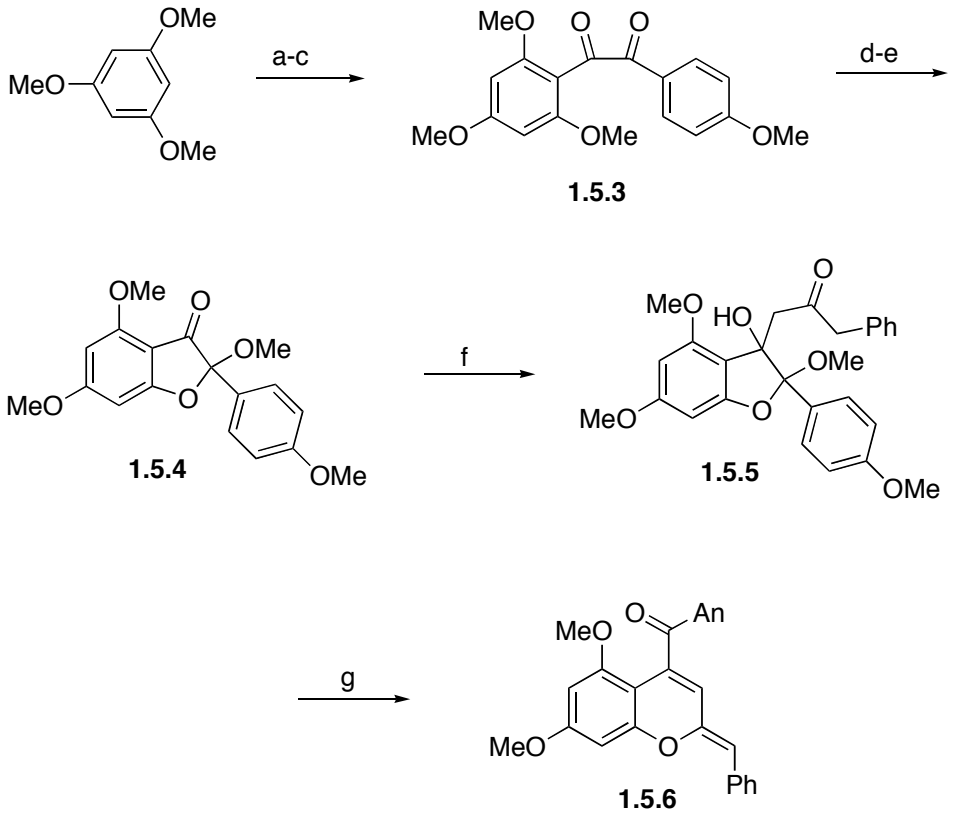
Previous work in the Magnus group began with the question as to whether enone **1.5.1**, under equilibrating acidic or basic conditions, would open to triarylcyclone **1.5.2** and close back onto the enone (Equation 1.5.1).[32] If so, would the *cis* or *trans* orientation of the aryl substituents predominate?



1.5.1 **1.5.2**

Equation 1.5.1 Equilibration *via* β-elimination hypothesis

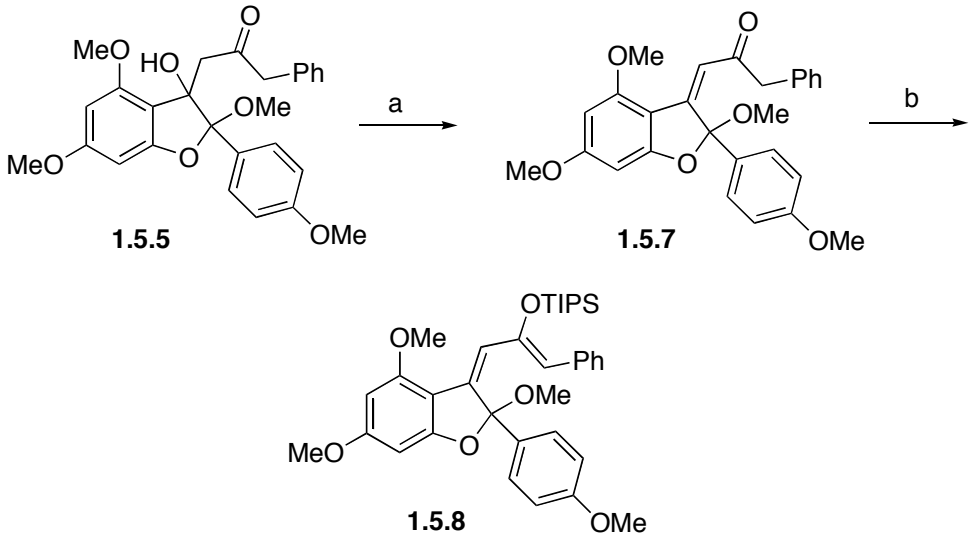
The synthesis of enone **1.5.1** began with iodination of 1,3,5-trimethoxybenzene followed by Sonogashira coupling of the iodo derivative with 4′-methoxyphenylacetylene (Scheme 1.5.1). Oxidation of the internal alkyne with $RuCl_3/NaIO_4$ introduced the diketone functionality in **1.5.3**. Treatment with BCl_3 followed by $(MeO)_3CH$ in MeOH and conc. H_2SO_4 yielded benzofuranone **1.5.4**. Addition of the dianion of benzyl methyl ketone gave tertiary alcohol **1.5.5**. It was believed that treatment under acidic conditions would eliminate the tertiary alcohol, form the oxonium ion and cyclization would occur to enone **1.5.1**. However, upon treatment with *p*-toluenesulfonic acid in benzene, the only product obtained was **1.5.6**. Therefore, it was decided that a step-wise approach to enone **1.5.1** would be investigated.



Conditions: (a) I_2, Red HgO, CH_2Cl_2, quant.; (b) 4-methoxyphenylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 80%; (c) $RuCl_3$, $NaIO_4$, MeCN, $CHCl_3$, H_2O, 60%; (d) BCl_3, CH_2Cl_2, 98%; (e) MeOH, $(MeO)_3CH$, H_2SO_4, quant.; (f) Benzyl methyl ketone, KH, *n*-BuLi, THF, then AcOH, 87%; (g) *p*-TsOH·H_2O, benzene, 75%.

Scheme 1.5.1 First attempt at cyclization

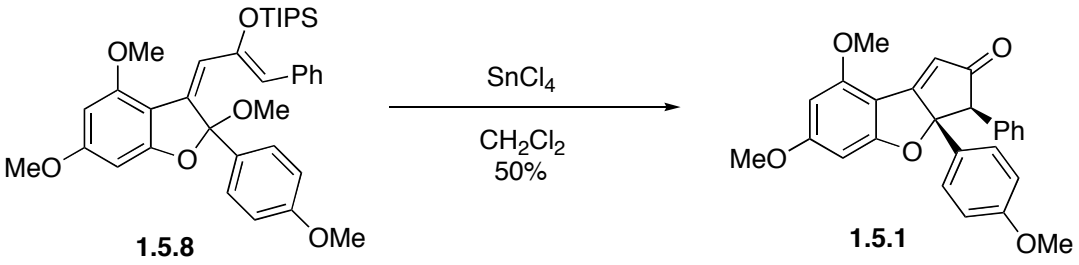
The tertiary alcohol was eliminated using Amberlyst 15® acidic ion-exchange resin to give enone **1.5.7** (Scheme 1.5.2). The ketone was converted into the triisopropylsilyl enol ether **1.5.8** and the system was set up to attempt the cyclization again.



Conditions: (a) Amberlyst 15 Acidic Resin, benzene, 94%; (b) NaH, TIPSCl, THF, 74%.

Scheme 1.5.2 Formations of TIPS enol ether

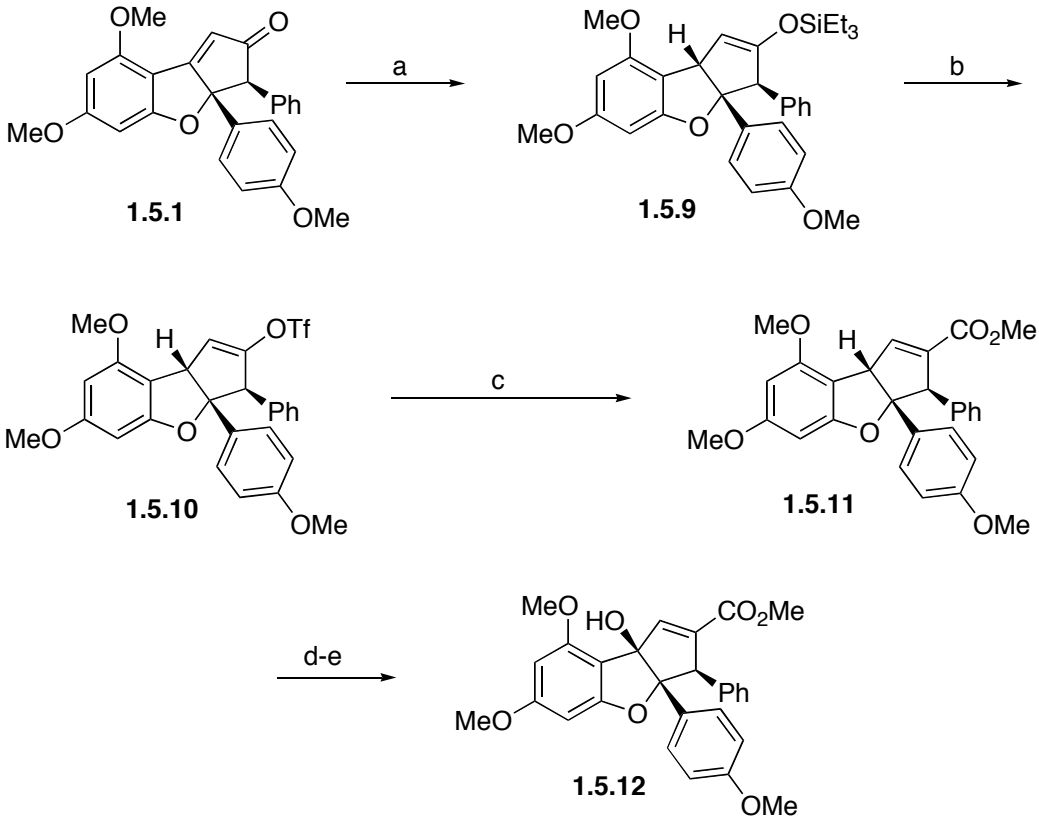
Treatment of the TIPS enol ether with $SnCl_4$ gave the cyclization product **1.5.1** in 50% yield and as a single diastereomer (Scheme 1.5.3). With the desired enone in hand, efforts to probe the elimination/conjugate addition hypothesis were initiated. Upon treatment with KO^{t}Bu/^{t}BuOH, the deep crimson color of cyclone **1.5.2** was observed, but cyclization of the phenol oxygen back onto the enone could not be induced under a variety of conditions. Thus, the hypothesis had been tested and been proven to be flawed.



Scheme 1.5.3 Nazarov or Mukaiyama aldol condensation

Enone **1.5.1** was then advanced further toward rocaglamide (Scheme 1.5.4). Silyl enol ether **1.5.9** was obtained *via* hydrosilylation using Wilkinson's catalyst. Desilylation with $BnMe_3NF$ and trapping of the enolate with N-phenyltrifluoromethanesulfonimide gave enol triflate **1.5.10**. Palladium catalyzed carbonylation of the vinyl triflate installed the ester functionality in **1.5.11**.

The oxidation of the benzylic position was next investigated. Numerous oxidants were screened, however, they failed to produce the desired product. The benzylic position was eventually oxidized to the peroxide upon exposure to ^tBuOOH in the presence of Darco G-60® activated carbon and K_2CO_3. Reduction of the peroxide with aluminum amalgam resulted in the formation of 1,2-anhydro methyl rocaglate **1.5.12**.



Conditions: (a) Et_3SiH, $RhCl(PPh_3)_3$, benzene, 88%; (b) $BnMe_3NF$, $PhNTf_2$, 4Å MS, THF, 74%; (c) CO (g), $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF, 82%; (d) *t*-BuOOH, DARCO, K_2CO_3, benzene, (e) Al(Hg), H_2O, THF, 36% (2 steps).

Scheme 1.5.4 Formation of 1,2-anhydro methyl rocaglate

Difficulties in obtaining sufficient amounts of alcohol **1.5.12** led to the abandonment of this route. However, this work was interesting in that the cyclization to the tricyclic core was completely diastereoselective.

1.6 References

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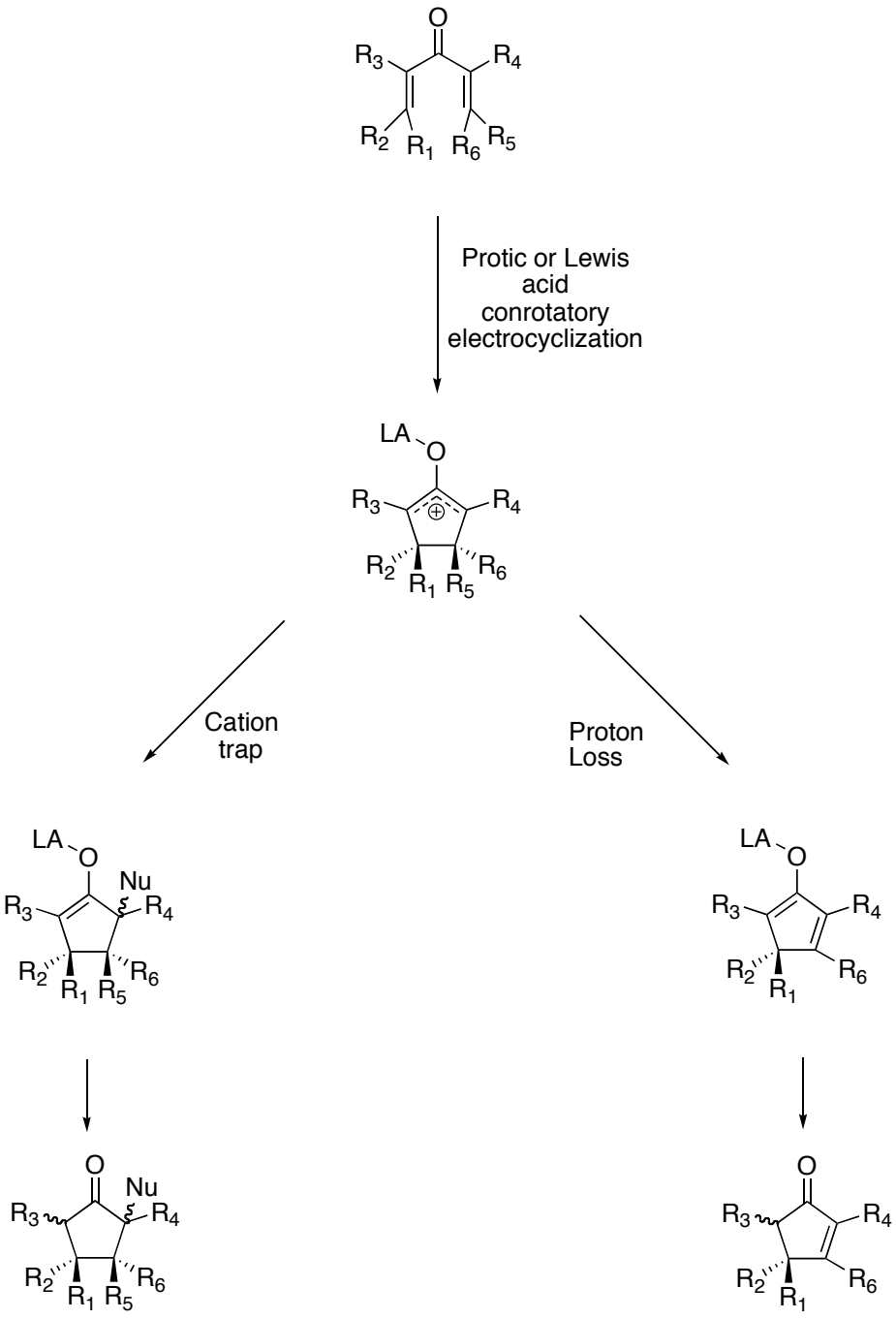
Chapter 2: Studies on the Total Synthesis of Rocaglamide

2.0 Introduction

Construction of the C-ring of the rocaglamides in a diastereoselective manner has been the focus of the Magnus group since the project began. A promising strategy for the formation of this ring has involved a Nazarov cyclization.[1-4] The Nazarov cyclization proceeds *via* formation of a pentadienyl cation, which under thermal conditions can undergo a conrotatory 4π-electron electrocyclization[5] forming an allylic cation. This cation can either be trapped by a nucleophile, or proton loss can occur to an alkene (Scheme. 2.0.1).



Scheme 2.0.1 The Nazarov cyclization

The Nazarov reaction has been extensively studied and found to be a useful reaction in a number of total syntheses.[6-8] All of the strategies described in this dissertation are focused on using a Nazarov cyclization to construct the C-ring of rocaglamide.

2.1 Extension of Previous Magnus Group Work

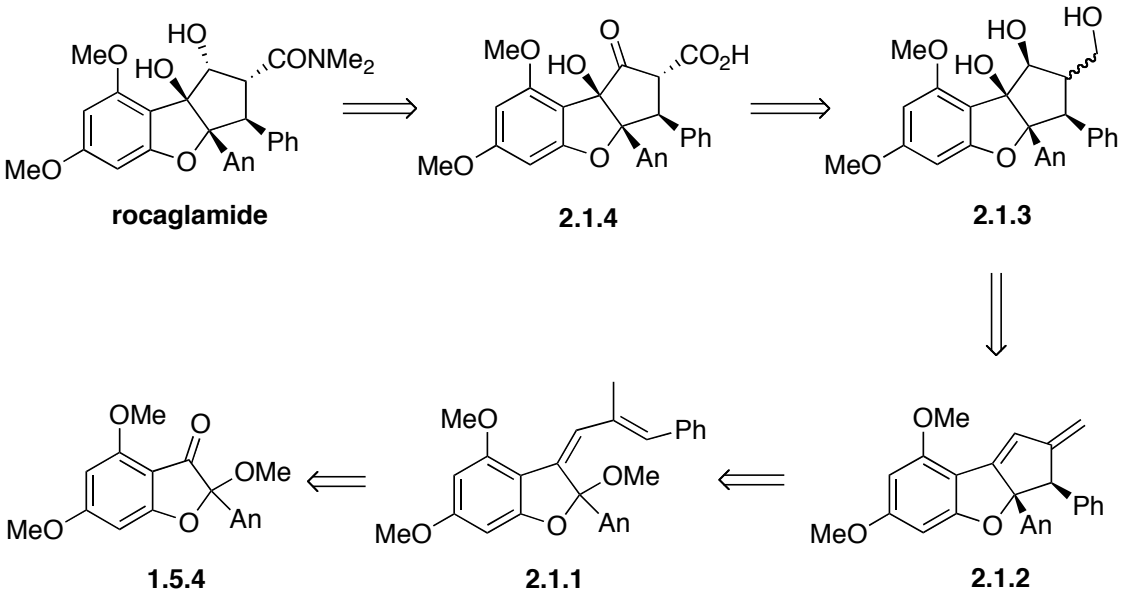
Due to problems encountered with the benzylic oxidation, as well as the fact that the previous route was becoming somewhat cumbersome, the route was changed slightly from the previous work done in the Magnus group. It was proposed that the carbon analogue **2.1.1** of the TIPS-enol ether **1.5.8** might also cyclize under Lewis acidic conditions to **2.1.2**. The exo-methylene compound **2.1.2** might be easier to advance to rocaglamide (Equation 2.1.1).

2.1.1 **2.1.2**

Equation 2.1.1 Proposed cyclization route to the C-ring

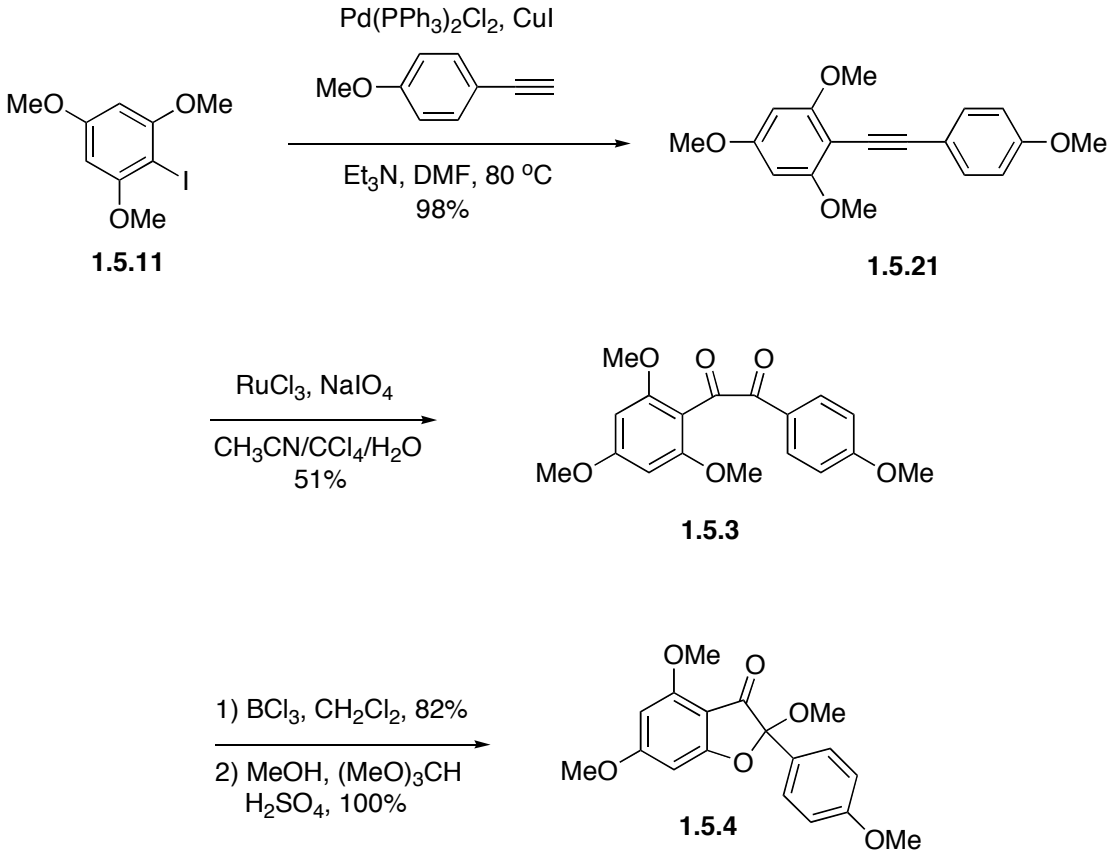
Rocaglamide was envisioned coming from Taylor's intermediate **2.1.4**, which in turn would come from triol **2.1.3** (Scheme 2.1.1). Dihydroxylation and hydroboration of **2.1.2** could yield **2.1.3**. The exo-methylene compound **2.1.2** could be synthesized *via*

Nazarov cyclization of **2.1.1**, which could be obtained from the alkylation/dehydration of **1.5.4**.



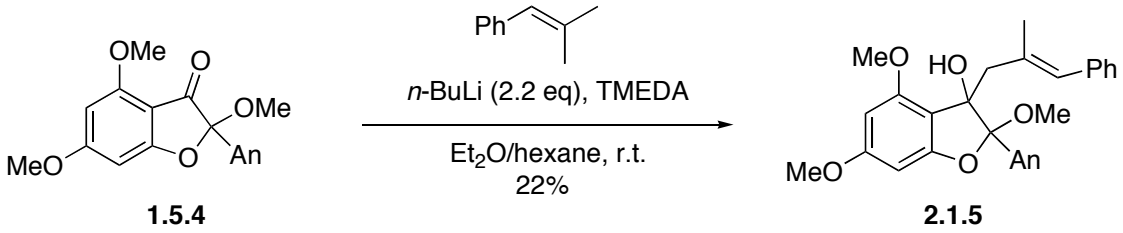
Scheme 2.1.1 Retrosynthetic Analysis

Ketone **1.5.4** was first synthesized using the previously reported route (Scheme 2.1.2).



Scheme 2.1.2 Synthesis of α-methoxy ketone

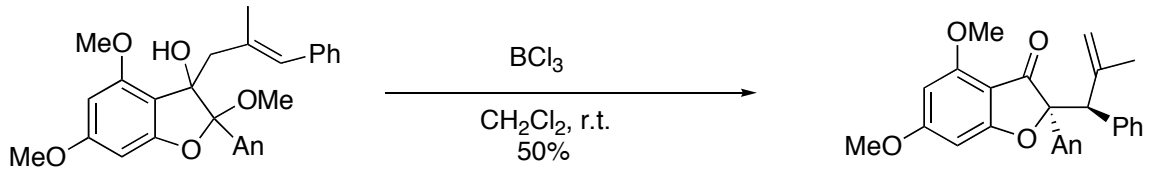
Ketone **1.5.4** was treated with the dianion of (2-methylprop-1-enyl)benzene with the expectation that the alkylation would occur at the γ-carbon. However, the major product of the reaction arose from alkylation at the α-carbon (relative to the phenyl). The desired tertiary alcohol was isolable, albeit in a poor yield of only 22% (Equation 2.1.2). Interestingly, the addition of only one equivalent of butyllithium gave identical results. Hence, whether or not the dianion was indeed being formed remains unclear.



1.5.4 **2.1.5**

Equation 2.1.2 Addition of dianion into ketone

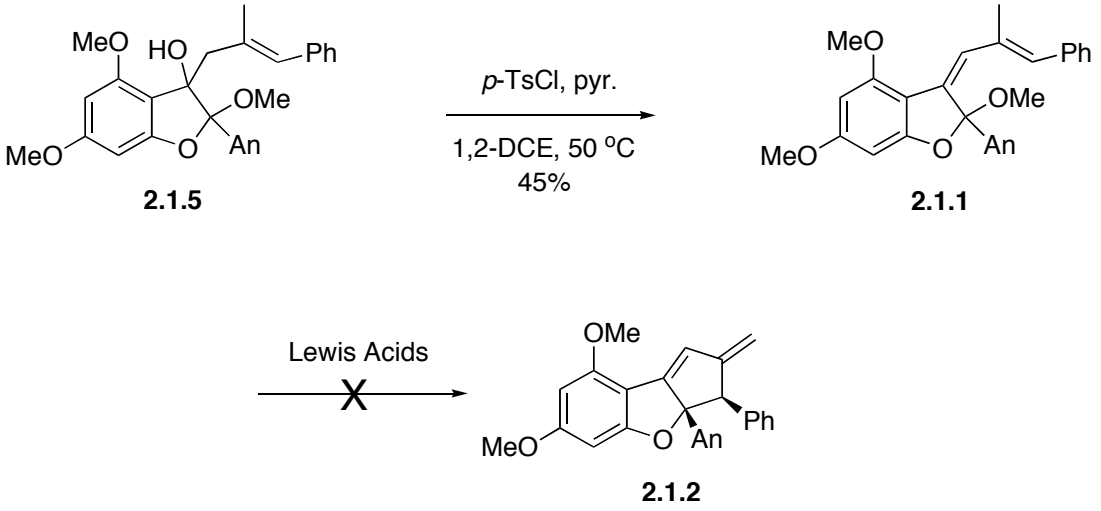
It was believed that upon treatment of **2.1.5** with a Lewis acid, dehydration would first occur to **2.1.1**. A Nazarov cyclization could follow to furnish the *exo*-methylene compound **2.1.2**. However, upon treatment with BCl_3 in CH_2Cl_2, cyclization and fragmentation occurred to ketone **2.1.6** (Equation 2.1.3). Unfortunately, the stereochemistry of the two aryl substituents, which was determined by X-ray crystallography, was entirely *trans* (See Appendix 1). Although the wrong configuration was initially obtained, it was thought that this configuration might only be the kinetic product of addition into the oxonium ion. Therefore, the establishment of equilibrating conditions was attempted using BCl_3 and heat to see if the reversal of the fragmentation could give the desired *cis* configuration of the aryl substituents. However, the harsher conditions only resulted in decomposition of the molecule.



2.1.5 **2.1.6**

Equation 2.1.3 Fragmentation to *trans* diaryl benzofuranone

Since dehydration and cyclization were not occurring in the same step as planned, a stepwise approach to **2.1.2** was considered. Dehydration was first performed using *p*-TsCl and pyridine in 1,2-DCE to obtain diene **2.1.1** in 45% yield (Scheme 2.1.3). Regrettably, treatment of **2.1.1** with $SnCl_4$ gave no reaction and BCl_3 resulted in extensive decomposition.

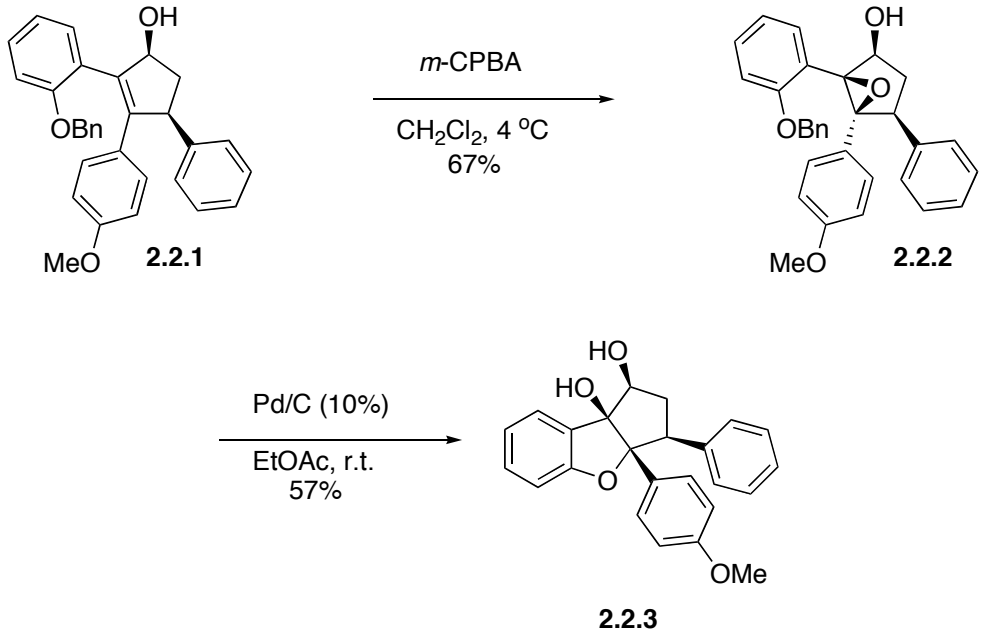


Scheme 2.1.3 Dehydration and attempted cyclization

This route was abandoned based on the failed attempts at inducing the cyclization, as well as the poor yield obtained on addition of the styrene fragment to obtain the tertiary alcohol. The exploration of alternate strategies ensued.

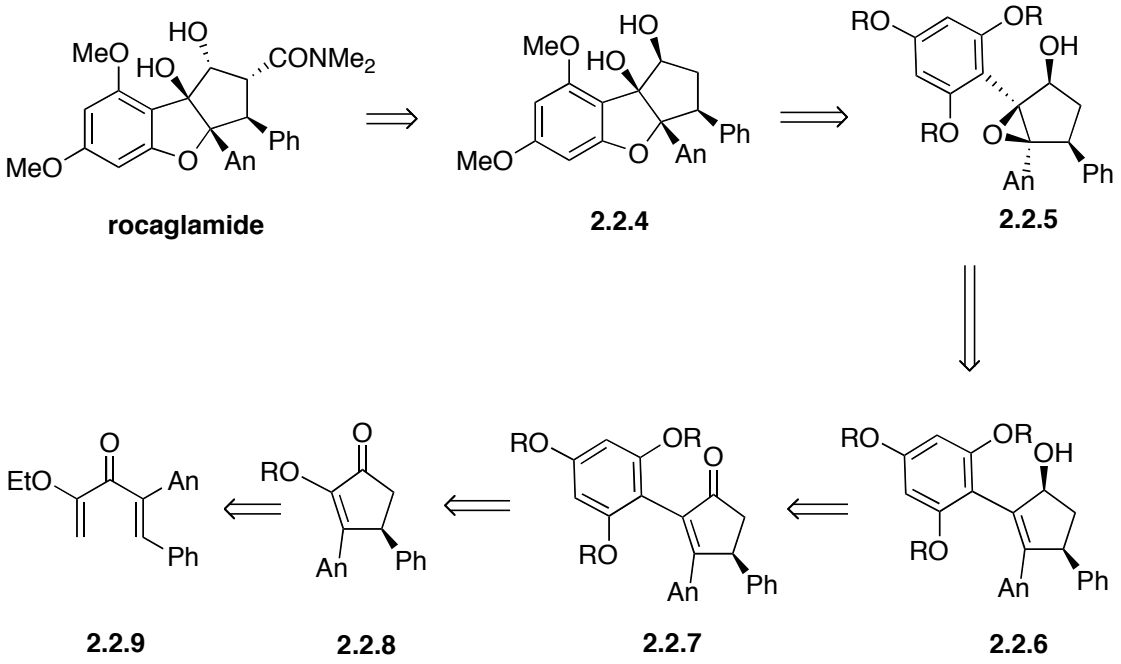
2.2 Epoxide Opening Strategy

A strategy that relied on an epoxide opening to construct the tetrahydro[*b*]benzofuran ring of rocaglamide was examined next. A Bayer research group reported in 2004 a stereoselective route to rocaglaol analogues using an epoxide opening strategy.[9] It was found that a directed epoxidation of allylic alcohol **2.2.1** using *m*-CPBA gave the required epoxide stereochemistry (**2.2.2**) (Scheme 2.2.1). Upon removal of the benzyl protecting group and opening of the epoxide by the phenolic oxygen, the benzofuran B-ring was formed with the desired *cis* configuration of the two aryl substituents on the C-ring (**2.2.3**). This strategy, however, was never applied to the synthesis of rocaglamide.



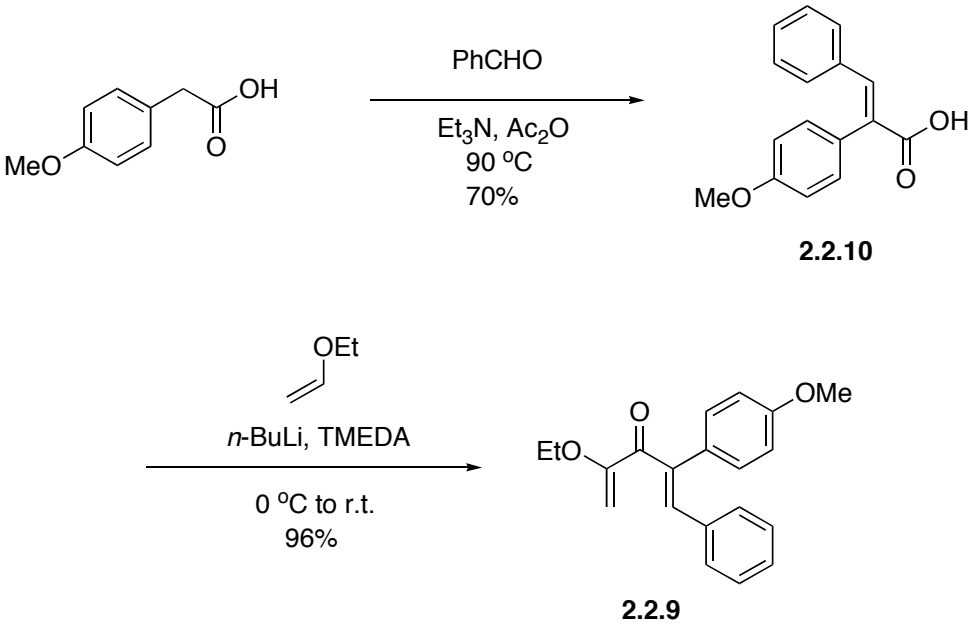
Scheme 2.2.1 Epoxide opening to close benzofuran

A retrosynthetic route to rocaglamide was devised based on the work of the Bayer group (Scheme 2.2.2). Rocaglamide was envisioned coming from diol **2.2.4**, which was an intermediate in Taylor's synthesis of rocaglamide. The diol could be obtained from an epoxide opening of **2.2.5** with the epoxide being generated from a directed epoxidation of allylic alcohol **2.2.6**.[10] The alcohol could come from reduction of ketone **2.2.7** which in turn is derived from the introduction of the A-ring to **2.2.8**. A Nazarov cyclization of **2.2.9** could be used to generate **2.2.8**. A promising feature of this strategy is the possibility of inducing enantioselectivity in the Nazarov cyclization by using a chiral catalyst.[11-13]



Scheme 2.2.2 Retrosynthetic analysis

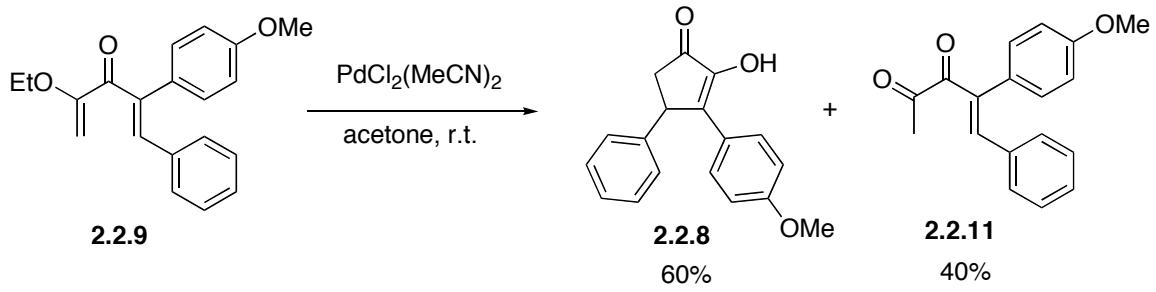
With a synthetic plan laid out, the synthesis of dienone **2.2.9** was begun (Scheme 2.2.3). Treatment of benzaldehyde and 4′-methoxyphenylacetic acid with Et_3N and Ac_2O gave α,β-unsaturated carboxylic acid **2.2.10** in 70% yield.[14,15] The acid was reacted with 3 equivalents of lithiated ethyl vinyl ether to yield dienone **2.2.9** in 96% yield. It is interesting to note that the deprotonation of ethyl vinyl ether occurred upon treatment with *n*-BuLi and TMEDA with warming to room temperature, whereas the use of *t*-BuLi for this deprotonation is widely reported in the literature. Using *n*-BuLi allowed for easier scale-up of this reaction and avoided the use of extremely pyrophoric *t*-BuLi.



Scheme 2.2.3 Formation of dienone for Nazarov cyclization

Substrate **2.2.9** was set up nicely for a Nazarov cyclization. α-Alkoxy dienones are highly reactive in Nazarov cyclizations because of the stabilizing effect that the

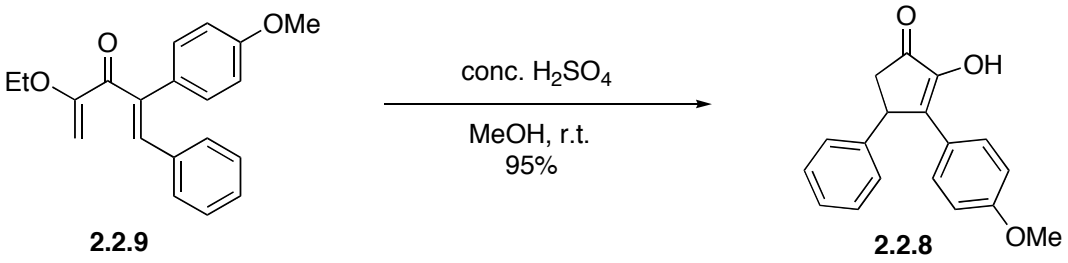
heteroatom has on the allylic cation.[16-19] Conditions reported by Tius for the cyclization of α-alkoxy dienones using catalytic palladium(II) were examined.[20] Upon treatment of dienone **2.2.9** with 1 mol% $PdCl_2(MeCN)_2$ in acetone, cyclized product **2.2.8** was obtained in 60% yield (Equation 2.2.1). The yield of this reaction varied widely because of competition between hydrolysis of the enol ether and cyclization to **2.2.8**. This was not surprising since Tius had reported that the hydrolysis of these types of enol ethers occurs under mild conditions.



2.2.9 **2.2.8** 60% **2.2.11** 40%

Equation 2.2.1 Palladium catalyzed cyclization

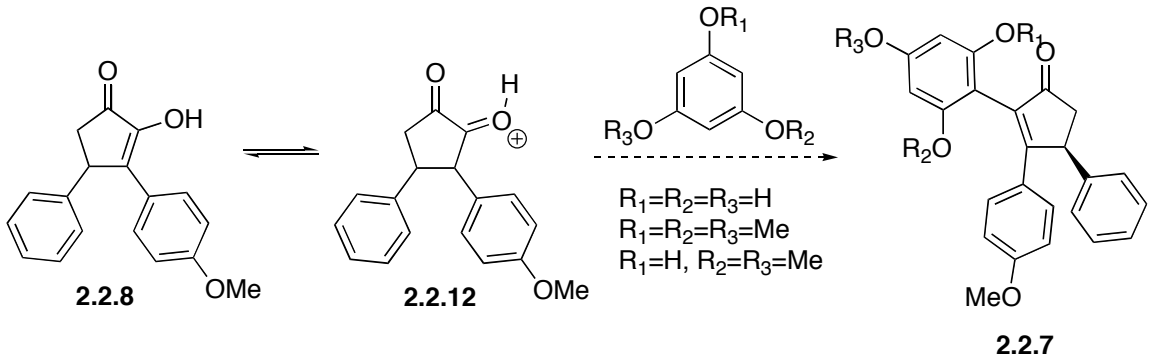
Owing to the problem of hydrolysis of the enol ether under palladium catalysis, a protic acid was examined to induce the cyclization. It was believed that even if the hydrolysis did occur, under highly acidic conditions the ketone would be in equilibrium with the enol tautomer and cyclization could still occur from that enol. Introduction of **2.2.9** to conc. H_2SO_4 in MeOH provided **2.2.8** in a highly reproducible yield of 95%, thereby proving our hypothesis (Equation 2.2.2).



Equation 2.2.2 Protic acid mediated cyclization

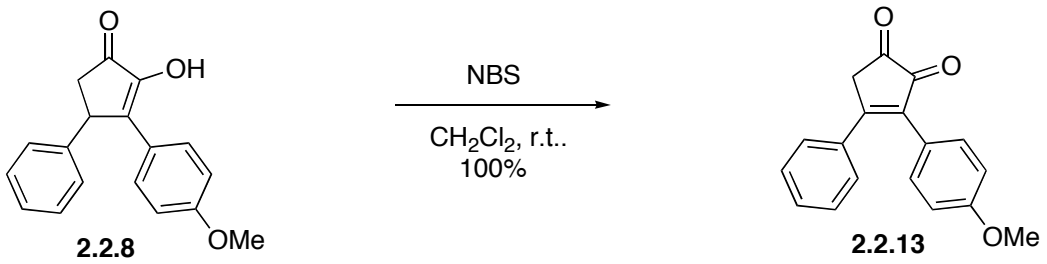
It was believed that the incorporation of the phloroglucinol derived A-ring of the rocaglamides could be accomplished by electrophilic aromatic substitution onto **2.2.8**. Under strongly acidic conditions, it may be possible to establish an equilibrium between **2.2.8** and α-diketone **2.2.12**. The diketone should be highly electrophilic for the aromatic ring to add into it (Scheme 2.2.4).

Numerous conditions were employed to perform this transformation. Various acids (conc. H_2SO_4, dry HCl(g), TfOH), solvents (MeOH, Et_2O) and nucleophiles (phloroglucinol, 3,5-dimethoxyphenol, 1,3,5-trimethoxybenzene) were screened, but **2.2.8** was recovered unchanged in all cases.



Scheme 2.2.4 Attempts at adding A-ring

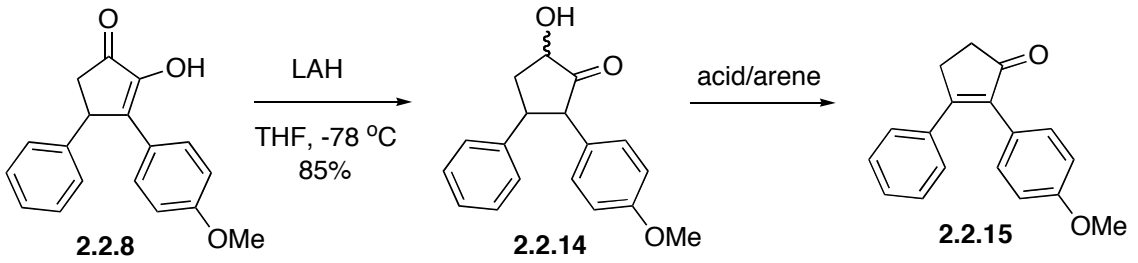
Since acidic conditions did not produce the desired result, it was believed that halogenation of the enol may enable the formation of an α-bromo ketone that might be reactive towards the electrophilic aromatic substitution. Treatment with NBS in CH_2Cl_2 at room temperature gave halogenation the enol, but elimination to cyclopentenone **2.2.13** also occurred under the reaction conditions (Equation 2.2.3).



2.2.8 **2.2.13**

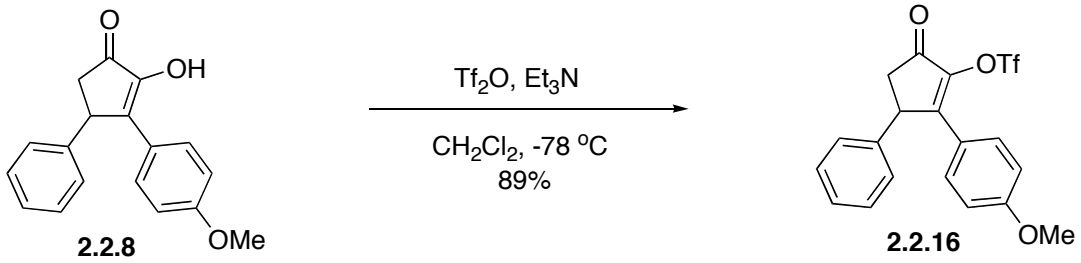
Equation 2.2.3 Halogenation of enol

The next approach to introducing the A-ring began with reduction of the ketone. This would shift the enol in **2.2.8** to the keto form, of which the phloroglucinol moiety might add into (Scheme 2.2.5). Upon treatment with LAH, ketone **2.2.8** was reduced to keto-alcohol **2.2.14** in good yield. When this compound was treated with a Lewis ($TiCl_4$, BF_3•OEt_2) or protic acid (conc. H_2SO_4, dry HCl) and a phenol (3,5-dimethoxyphenol, phloroglucinol), no incorporation of the aromatic group was observed. The sole product obtained was cyclopentenone **2.2.15**.[21,22] Treatment of **2.2.14** under basic conditions, with 2 equivalents of lithiated 1,3,5-trimethoxybenzene, produced an intractable mixture of products.



Scheme 2.2.5 Attempted addition of A-ring to keto-alcohol

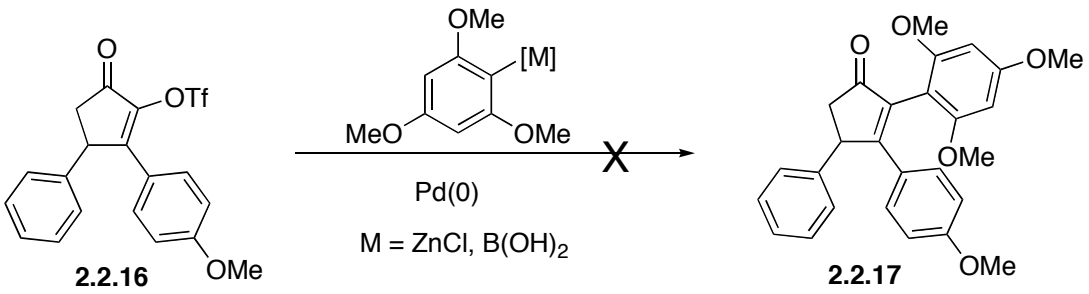
Approaches to incorporate the A-ring into the system did not work as planned. Therefore, a transition metal-catalyzed coupling reaction to install the A-ring was investigated. Enol **2.2.8** was converted to enol triflate **2.2.16** in 89% yield with trifluoromethanesulfonic anhydride and triethylamine (Equation 2.2.4).



Equation 2.2.4 Formation of enol triflate

Coupling of 1,3,5-trimethoxybenzene with the enol triflate **2.2.16** was next attempted (Equation 2.2.5). The palladium catalyzed Suzuki cross coupling[23] of 2,4,6-trimethoxyphenylboronic acid[24] with the enol triflate was examined first. After screening numerous conditions and palladium catalysts, none of the desired product was ever generated. The starting enol triflate along with the deboronated aromatic were recovered

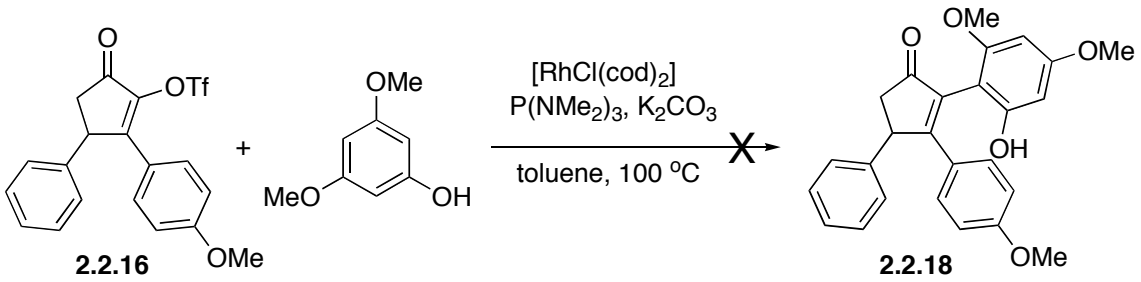
under the various conditions. To avoid the proto-deboronation observed under Suzuki cross coupling conditions, a Negishi coupling[25] was attempted using the zincated trimethoxybenzene. The conditions screened for this transformation resulted in an intractable mixture of compounds.



Equation 2.2.5 Attempted coupling of enol triflate

Attempts at a direct coupling of 1,3,5-trimethoxybenzene, 3,5-dimethoxyphenol or phloroglucinol and the enol triflate with palladium catalysis only returned starting material.

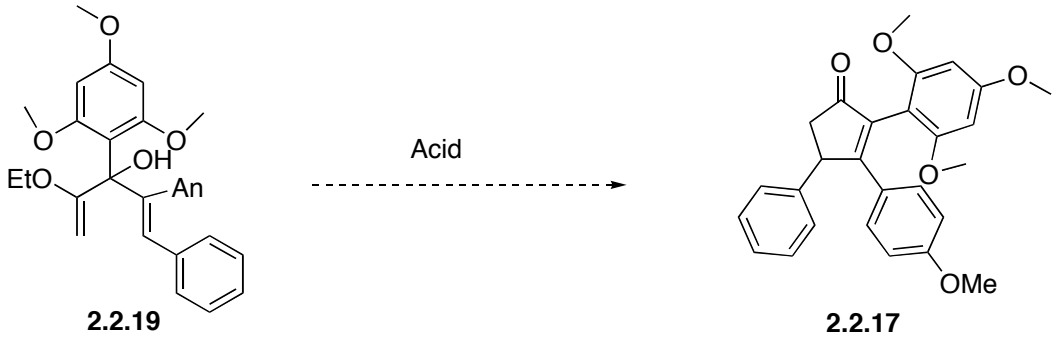
The directed ortho-arylation of phenols using a rhodium catalyst was also explored.[27,28] Attempted coupling of 3,5-dimethoxyphenol and **2.2.16** using $[RhCl(cod)_2]$ and HMPT in toluene resulted in unidentifiable products (Equation 2.2.6).



Equation 2.2.6 Directed ortho-arylation attempt

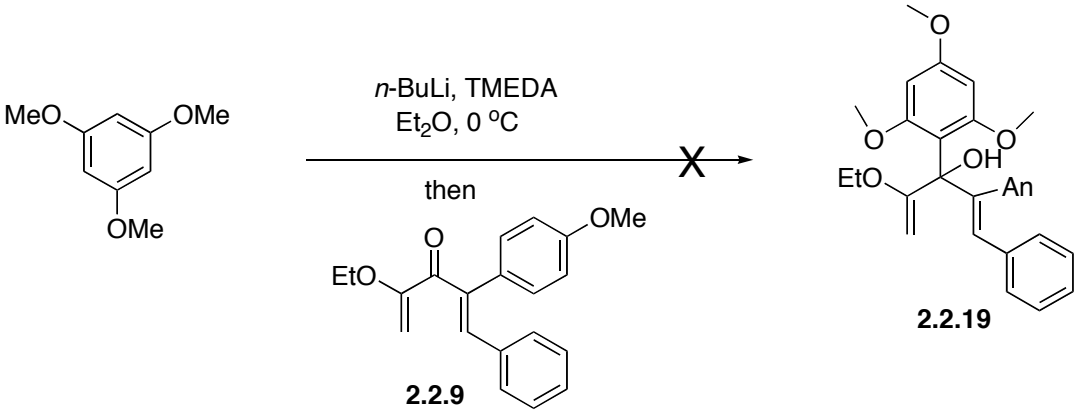
It was assumed that the oxidative addition into the carbon-triflate bond was causing the low reactivity of the substrate. Sorensen has previously documented problems associated with oxidative addition of palladium(0) into enol triflates of cyclopentenones.[26]

At this point, the coupling strategy to the enol triflate was abandoned and the strategy was again reexamined. It was thought that a more straightforward way to introduce the aromatic could be prior to the cyclization event. It was believed a compound such as **2.2.19** could be cyclized under acidic conditions to the desired cyclopentenone **2.2.17** (Equation 2.2.7).



Equation 2.2.7 Nazarov cyclization to obtain **2.2.17**

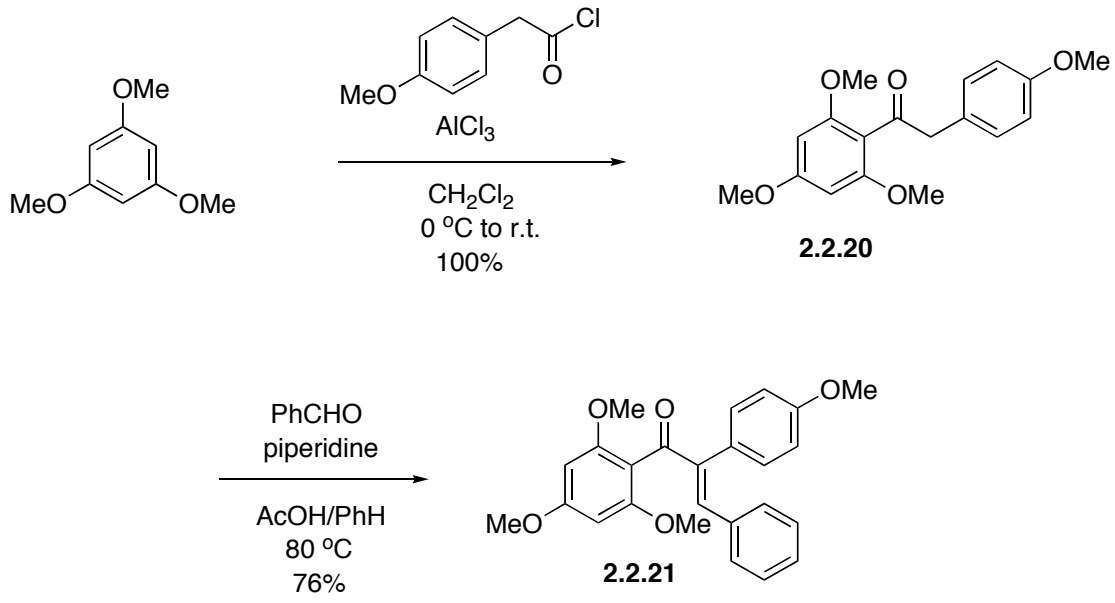
To synthesize **2.2.19**, the 1,2-addition of lithiated 1,3,5-trimethoxybenzene to dienone **2.2.9** was attempted (Equation 2.2.8). Treatment of 1,3,5-trimethoxybenzene with *n*-BuLi and TMEDA in Et_2O followed by the addition of dienone **2.2.9** gave an intractable mixture. A number of conditions were screened, but **2.2.19** was never observed.



Equation 2.2.8 Addition of lithiated 1,3,5-trimethoxybenzene to dienone

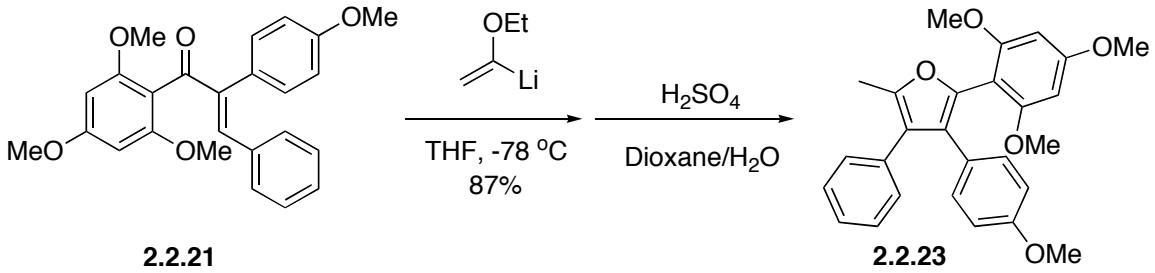
Some difficulties in this addition may have been occurring due to the hydrolysis of the enol ether while the dienone sat on the bench. Therefore, incorporation of the enol ether at the last step in the dienol synthesis was examined to avoid this problem.

A slightly different route needed to be taken to accomplish this (Scheme 2.2.6). Friedel-Crafts acylation of 1,3,5-trimethoxybenzene with 4′-methoxyphenylacetyl chloride gave ketone **2.2.20** in quantitative yield. Knoevenagel condensation with benzaldehyde produced enone **2.2.21** in good yield.



Scheme 2.2.6 Synthesis of enone **2.2.21**

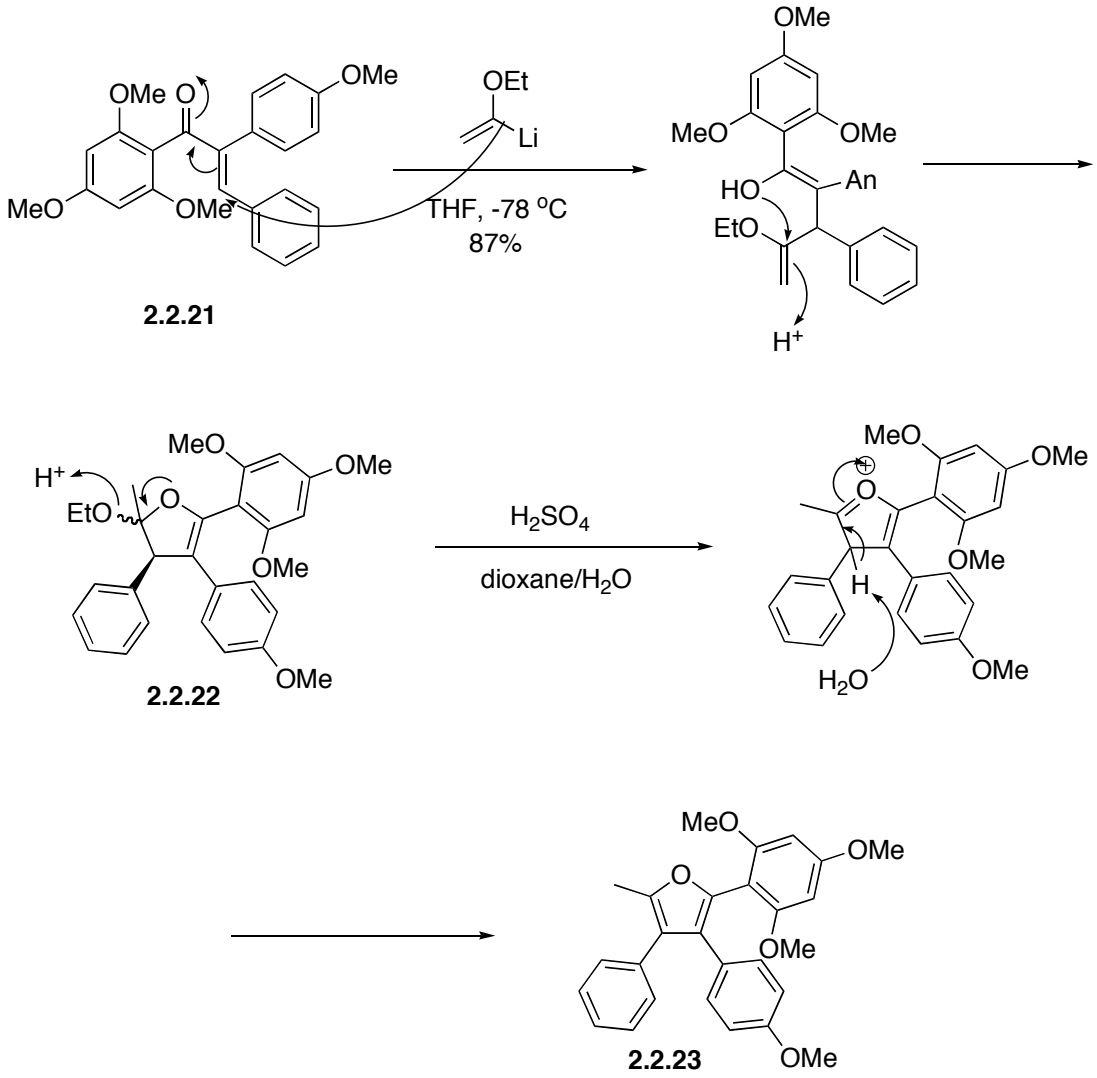
Enone **2.2.21** was treated with lithiated ethyl vinyl ether and one product was observed by TLC (Scheme 2.2.7). It seemed reasonable at first that the desired dienol had been produced since the crude NMR spectrum showed the vinylic protons of the ethyl vinyl ether incorporated into the product and a crude IR spectrum showed an –OH stretch. However, upon purification by column chromatography, the initial product had disappeared and a new compound had formed. This product eluted as a mixture of two compounds that appeared to be diastereomers. More importantly, the alcohol stretch was not present and the vinylic protons were gone. The identity of the product at this point was unclear, until treatment with H_2SO_4 in dioxane gave furan **2.2.23**. The lack of an alcohol or carbonyl stretch in the IR spectrum and the observance of a methyl substituent by NMR gave credence to this structure.



2.2.21 **2.2.23**

Scheme 2.2.7 Formation of furan **2.2.23**

Furan **2.2.23** arose from the 1,4-addition of ethyl vinyl ether to enone **2.2.21**, followed by acid catalyzed ring closure onto the enol ether (Scheme 2.2.8). Elimination of ethanol occurred upon treatment with acid to give furan **2.2.23**.



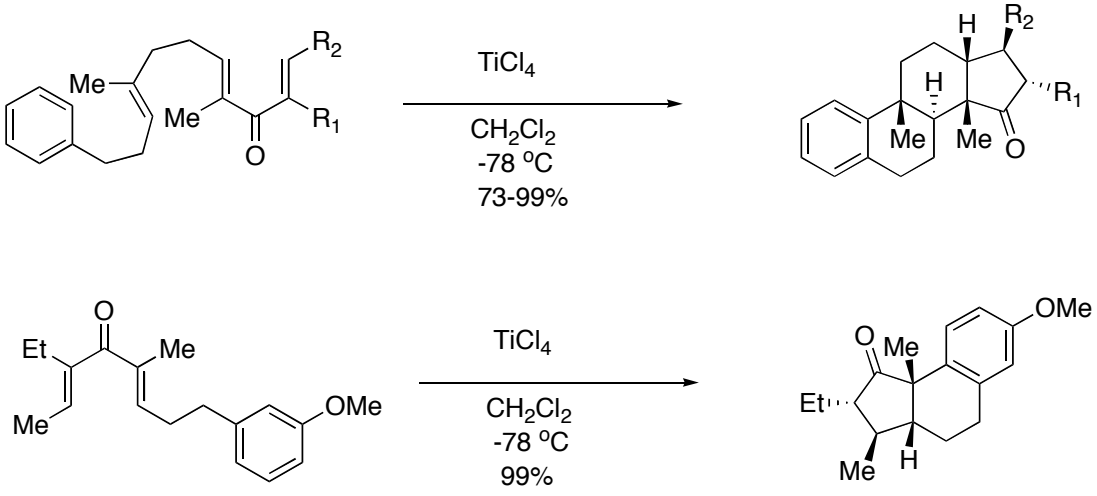
Scheme 2.2.8 Mechanism of formation of furan **2.2.23**

Treatment of the lithiated ethyl vinyl ether with $CeCl_3$ prior to addition to the enone did not promote the 1,2-addition and again the 1,4-addition product was obtained.

The epoxide opening route was also abandoned at this point as the incorporation the A-ring into the system proved more difficult than anticipated. A number of methods were explored, but with little success.

2.3 Interrupted Nazarov Strategy

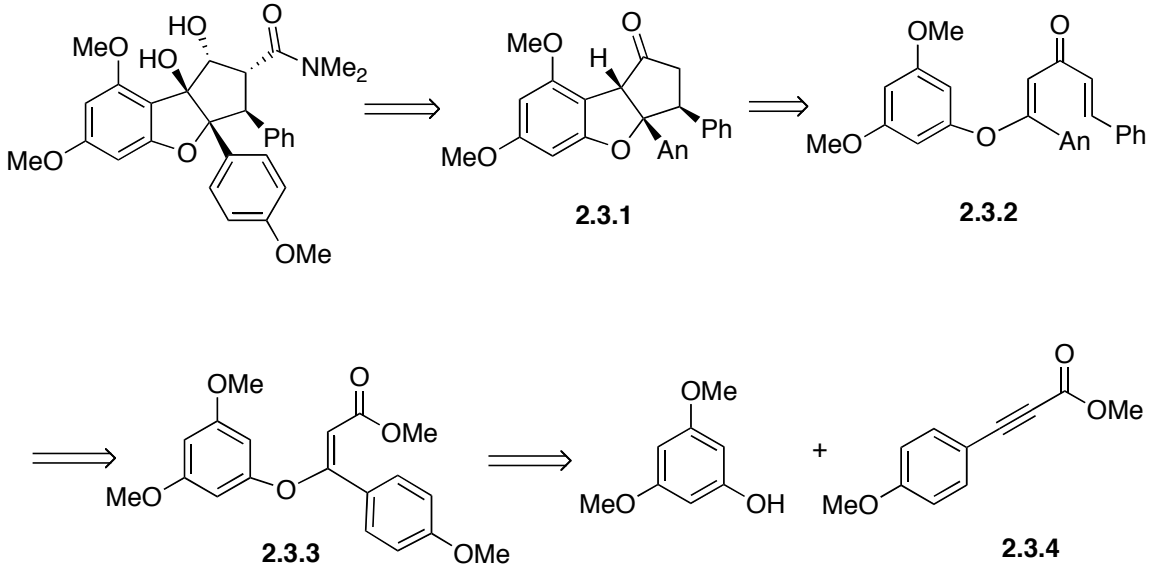
The focus of the project next shifted to a route that could potentially be very direct to the rocaglamide skeleton. Taking inspiration from work published by West, it was believed that construction of the B- and C-rings of rocaglamide could be accomplished in a single step. West had shown that dienones containing a tethered aromatic ring could undergo a Nazarov cyclization followed by trapping of the allylic cation by the aromatic to give polycyclic compounds (Scheme 2.3.1).[29-31] When the allylic cation is trapped by a nucleophile subsequent to a Nazarov cyclization, it is termed an "interrupted" Nazarov. These transformations were high yielding and completely diastereoselective.



Scheme 2.3.1 West's interrupted Nazarov cyclizations

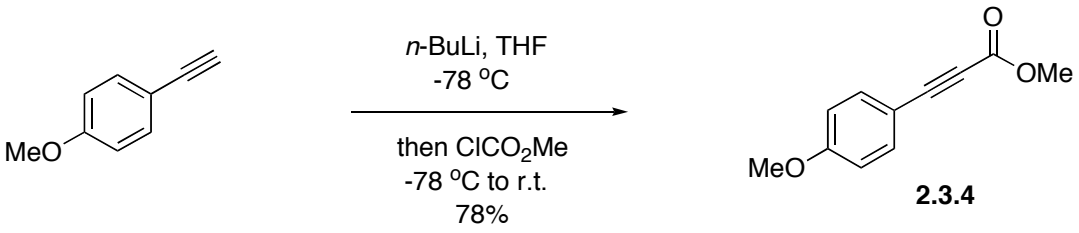
Although West used the tethered aromatics to form 6-membered rings upon capture of the allylic cations, we were hopeful that the same principle could operate for the formation of the 5-membered furan B-ring of rocaglamide.

The retrosynthetic plan was laid out as follows (Scheme 2.3.2). Rocaglamide was envisioned coming from the cyclopentanone **2.3.1** that could be made by an interrupted Nazarov reaction of dienone **2.3.2**. This dienone could be synthesized by Horner-Wadsworth-Emmons olefination of the β-keto phosphonate derived from ester **2.3.3**. This ester would result from the conjugate addition of 3,5-dimethoxyphenol to activated acetylene **2.3.4**.



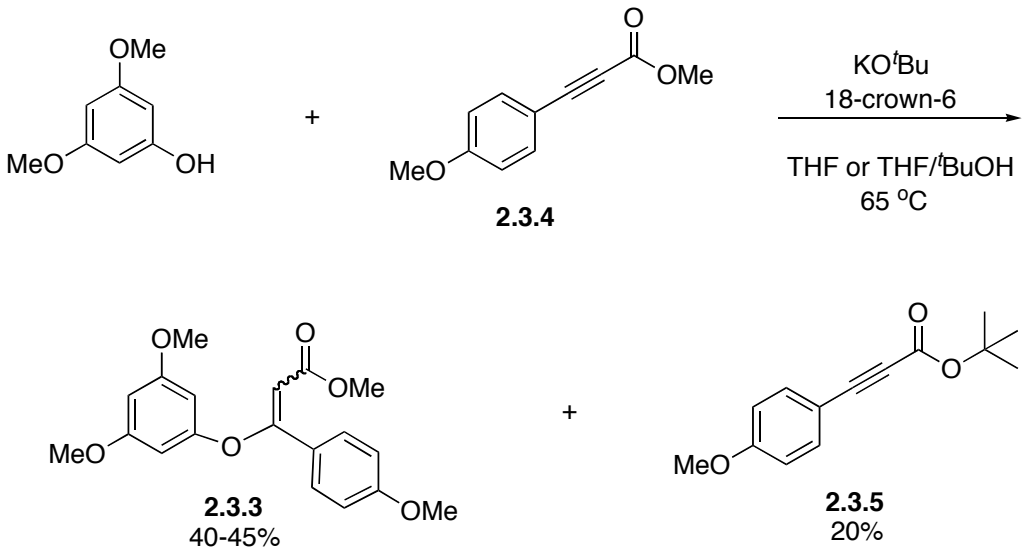
Scheme 2.3.2 Retrosynthetic analysis

The synthesis started with the formation of activated ester **2.3.4**. This ester was readily available by treatment of lithiated 4′-methoxyphenylacetylene with methyl chloroformate in 78% yield (Equation 2.3.1).



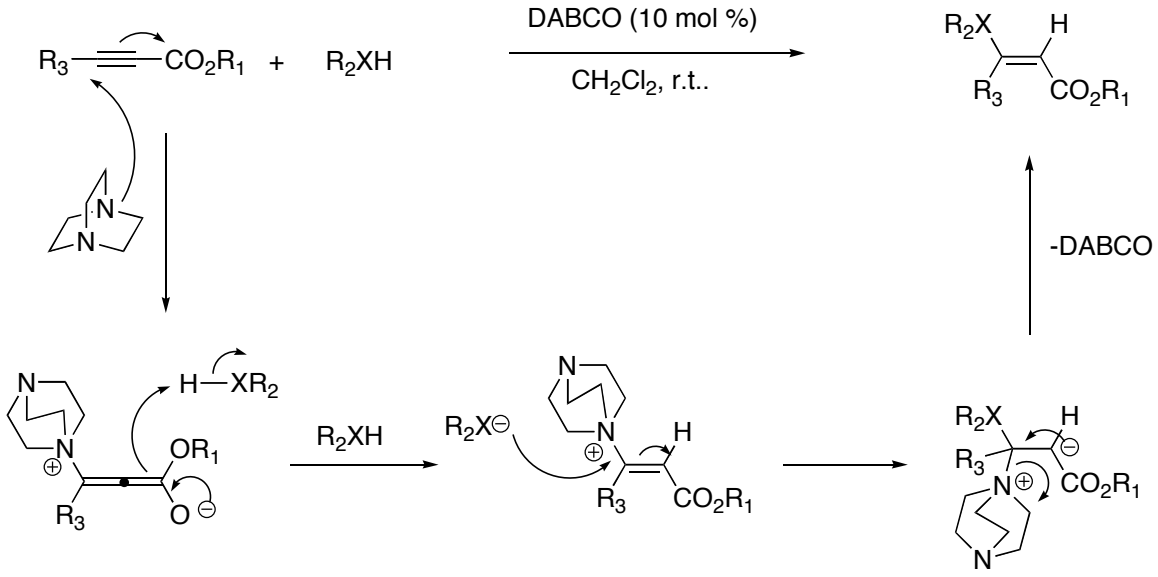
Equation 2.3.1 Formation of activated acetylene

Conditions to promote the conjugate addition of a phenol to this acetylene were examined. This transformation was first attempted under basic conditions since these conditions are well-precedented.[32-34] Treatment of 3,5-dimethoxyphenol with potassium *tert*-butoxide and 18-crown-6 in THF at 0 °C, followed by the addition of acetylene **2.3.4** and heating to 65 °C, yielded the desired 1,4-adduct **2.3.3** as a mixture of double bond isomers in 41% yield. *tert*-Butyl ester **2.3.5** was also formed in 20% yield (Equation 2.3.2). The formation of the *tert*-butyl ester was believed to arise from the lack of protons available to protonate the enolate formed upon 1,4-addition of the phenol. A mixture of *t*-BuOH and THF prevented the formation of **2.3.5**, but the yield of **2.3.3** still remained around 45%.



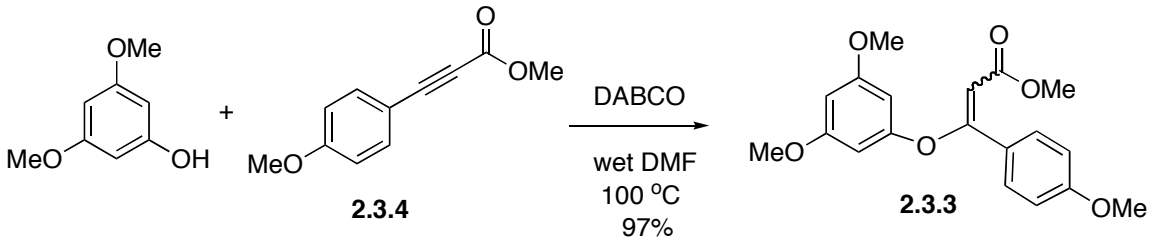
Equation 2.3.2 Addition of phenolate to activated acetylene

Due to less than satisfactory yields of **2.3.3**, a search for an alternative method to improve the conjugate addition ensued. In 2006, a paper was published using DABCO as a catalyst for the 1,4-addition of nucleophiles to activated alkynes.[35] The proposed mechanism states that conjugate addition of DABCO to the substrate activates the β-position toward nucleophilic addition (Scheme 2.3.3). Attack of the nucleophile at the β-position gives a zwitterionic intermediate, which upon elimination of DABCO, generates the β-substituted enone.



Scheme 2.3.3 Mechanism of DABCO catalyzed conjugate addition

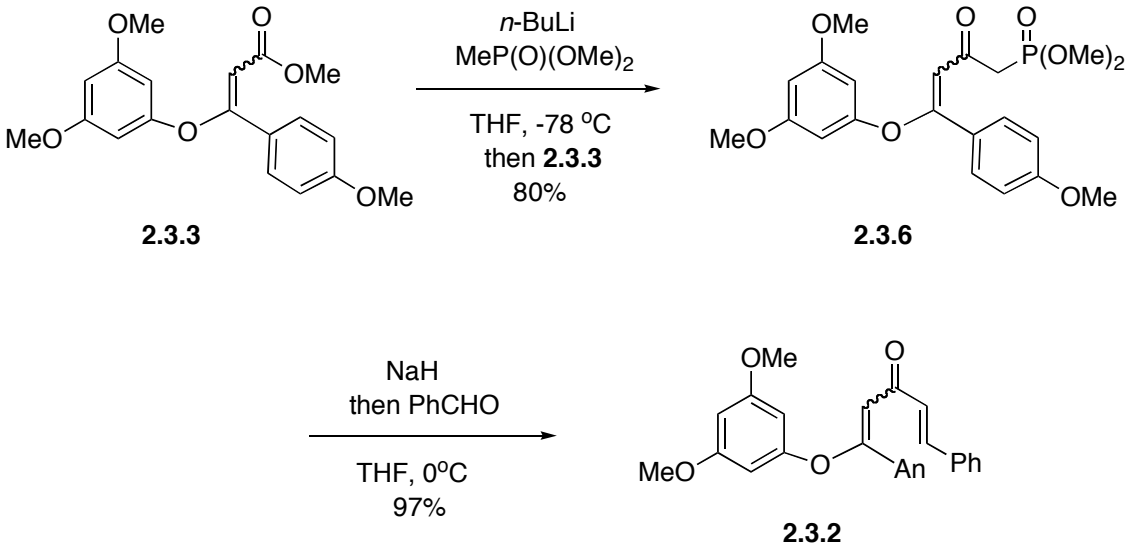
Using this method, it was found that heating 3,5-dimethoxyphenol and acetylene **2.3.4** in wet DMF with a catalytic amount of 1,4-diazabicyclo[2.2.2]octane resulted in the formation of desired enone **2.3.3** in quantitative yield (Scheme 2.3.4). The product was isolated as a 5:1 mixture of double bond isomers, where the major isomer was believed to be the *trans* compound, with respect to the anisyl and ester groups. This assumption was based on comparison of the chemical shift of the enone α-proton to similar substrates.[35]



Scheme 2.3.4 Conjugate addition using DABCO

The mixture of double bond isomers was of little concern at this point since isomerization of double bonds under the conditions used to induce a Nazarov cyclization is known.[8] The desired stereochemistry of the two aryl substituents upon cyclization might still be obtained because of this isomerization.

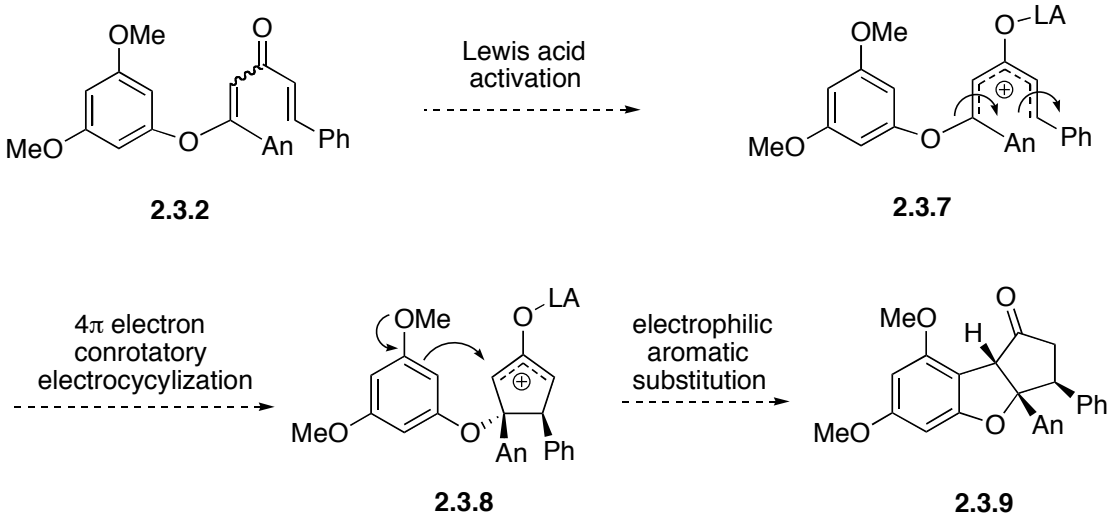
Ester **2.3.3** was treated with lithiated dimethyl methylphosphonate to obtain β-keto phosphonate **2.3.6** as a mixture of double bond isomers (Scheme 2.3.5). Horner-Wadsworth-Emmons olefination was carried out using sodium hydride and benzaldehyde to deliver dienone **2.3.2**.



Scheme 2.3.5 Formation of the dienone for cyclization

At this point the interrupted Nazarov cyclization hypothesis could be tested. It was believed that treatment with a Lewis acid would cause the formation of pentadienyl cation **2.3.7** (Scheme 2.3.6). A conrotatory electrocyclization could then take place to

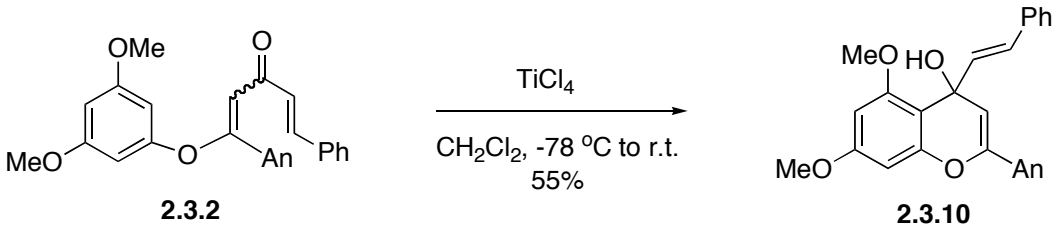
allylic cation **2.3.8**, which may be trapped by the electron rich aromatic, *via* electrophilic aromatic substitution, to provide the tricyclic core of rocaglamide **2.3.9**.



2.3.2 **2.3.7** **2.3.8** **2.3.9**

Scheme 2.3.6 Proposed mechanism of the interrupted Nazarov cyclization

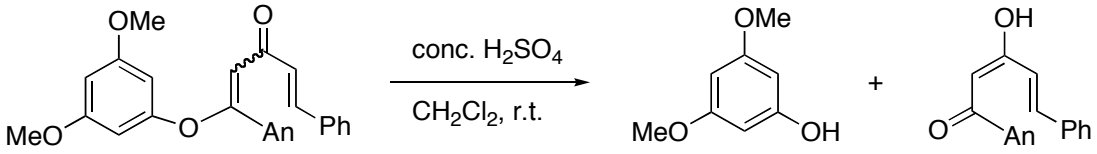
When dienone **2.3.2** was introduced to $TiCl_4$ in dichloromethane at -78 ºC followed by warming to room temperature, none of cyclopentanone **2.3.9** was observed. Cyclization of the aromatic onto the carbonyl of the dienone occurred instead, yielding **2.3.10** (Equation 2.3.3). This was not surprising since formation of the 6-membered ring was thought to be a possible outcome under these conditions.



2.3.2 **2.3.10**

Equation 2.3.3 Attempted Nazarov cyclization

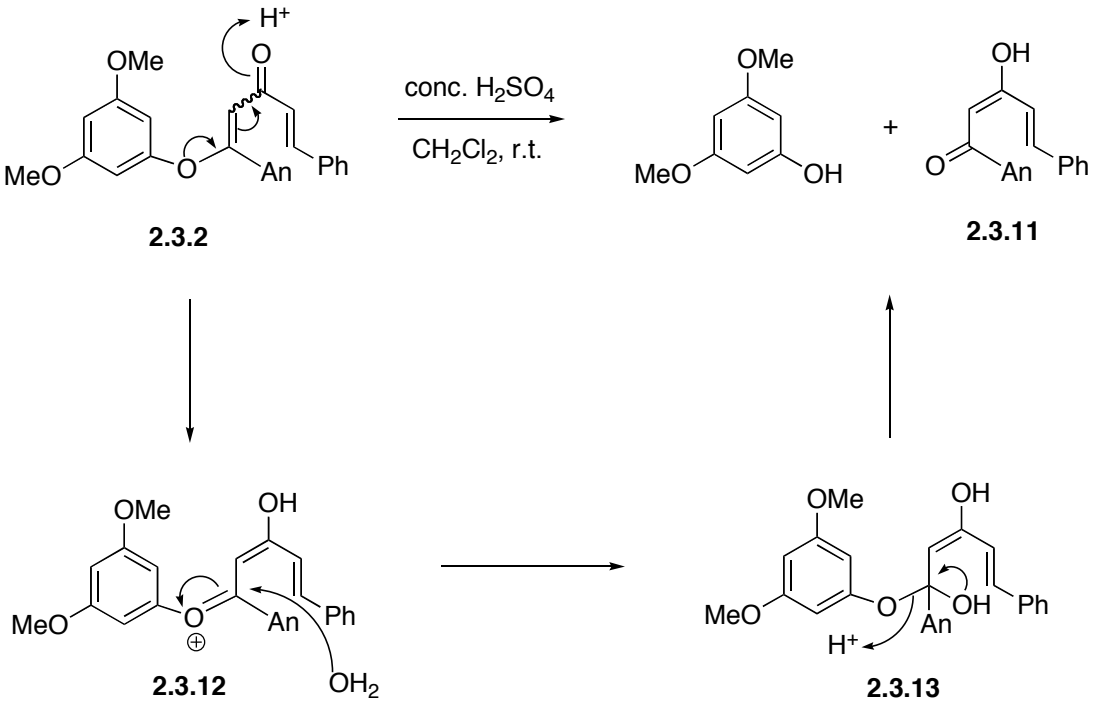
Treatment of dienone **2.3.2** with concentrated H_2SO_4 in CH_2Cl_2, resulted in fragmentation of the molecule, and 3,5-dimethoxyphenol and ketone **2.3.11** were the only observable products (Equation 2.3.4).



2.3.2 **2.3.11**

Equation 2.3.4 Fragmentation under protic acid conditions

The fragmentation occurred first by protonation of the carbonyl group and formation of oxonium ion **2.3.12** (Scheme 2.3.7). Addition of water into the oxonium ion gave acetal **2.3.13**. Finally, fragmentation of the acetal occurred with loss of 3,5-dimethoxyphenol to form ketone **2.3.11**.

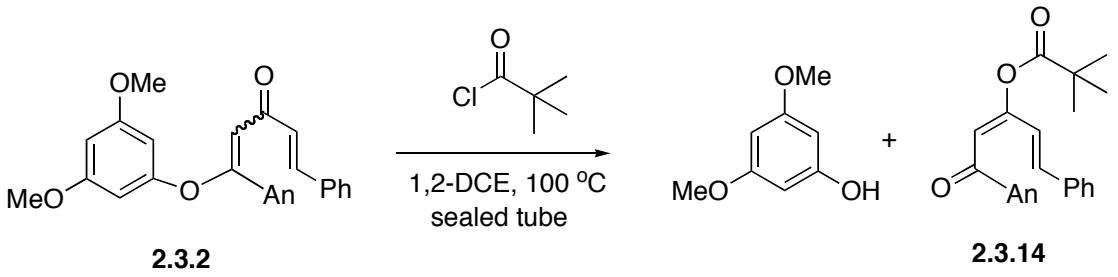


Scheme 2.3.7 Mechanism of fragmentation

Since cyclization onto the carbonyl of the aromatic group was happening under Lewis acidic conditions and fragmentation occurring under protic acid conditions, a way to possibly overcome these issues could be *via* acylation. It was believed that acylation of the carbonyl with a bulky acylating agent such as trimethylacetyl chloride, might prevent the addition of the aromatic into the carbonyl due to steric hindrance. Additionally, the anhydrous conditions might prevent the fragmentation seen with protic acids.

This hypothesis was tested by heating dienone **2.3.2** and trimethylacetyl chloride in 1,2-DCE at 100 ºC until all of the starting material was consumed (Equation 2.3.5). Unfortunately, the acylated fragmentation product **2.3.14** and 3,5-dimethoxyphenol were

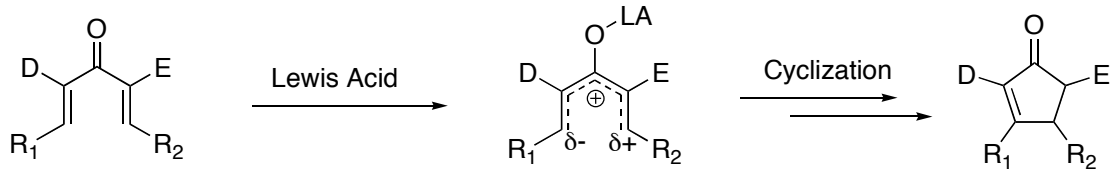
the only products obtained. These products could potentially arise from chloride addition into the oxonium ion after acylation of the carbonyl, which upon aqueous workup, fragmented to ketone **2.3.14**.



Equation 2.3.5 Acylation and fragmentation of dienone

A strategy was needed to make the dienone more reactive toward cyclization. The activation energy of the Nazarov cyclization needed to be lowered to encourage the cyclization to occur over attack at the carbonyl.

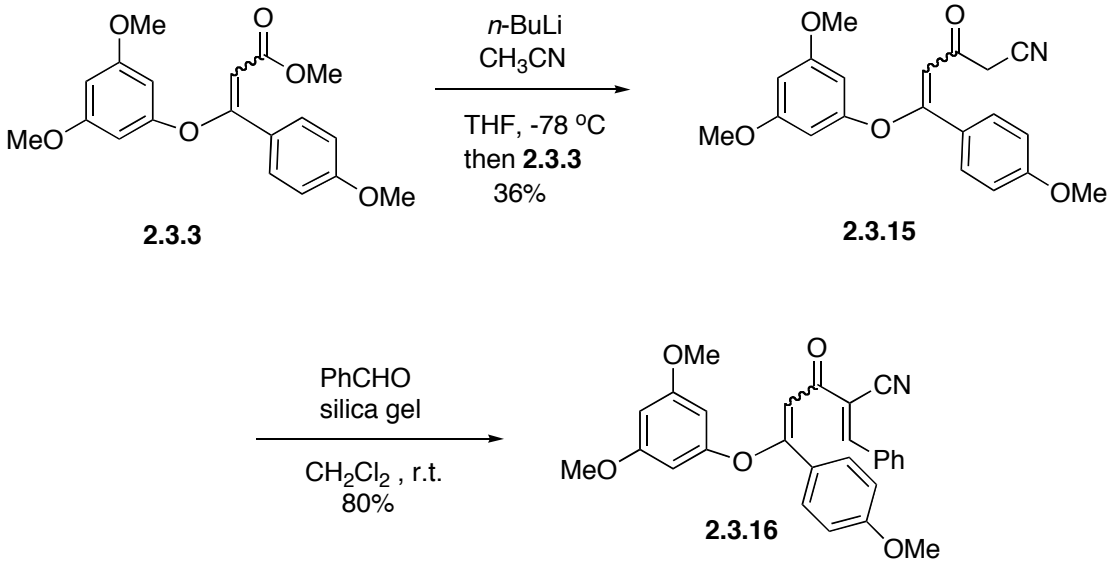
Methods of decreasing the activation energy of a Nazarov cyclization are known by incorporating an electron-withdrawing group at the α-position of one of the enones (Scheme 2.3.8).[36,37] Placing an electron-withdrawing group at one α-position of the dienone makes this double bond more electrophilic, while the other double bond is more nucleophilic. This polarization lowers the activation energy of the Nazarov cyclization, and it can be induced by weak Lewis acids such as $Cu(OTf)_2$. Weak protic acids, like acetic acid, have also been reported to induce a Nazarov cyclization of highly polarized dienones.



(D= electron-donating group, E= electron-withdrawing group)

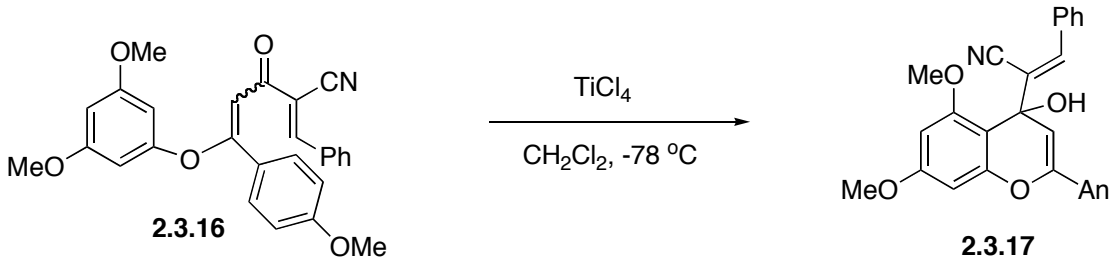
Scheme 2.3.8 Polarization of dienone for Nazarov cyclization

To determine if polarization of the dienone would solve the problems that had previously been encountered, a dienone with an electron-withdrawing group at the α-position was synthesized. A nitrile was introduced at the α-position starting from ester **2.3.3**. The addition of lithiated acetonitrile to methyl ester **2.3.3** at -78 ºC yielded 36% of the desired keto-nitrile **2.3.15**. Treatment of **2.3.15** with benzaldehyde and silica gel in dichloromethane produced α-cyano dienone **2.3.16** in good yield.



Scheme 2.3.9 Synthesis of α-cyano dienone

Unfortunately, polarization of the dienone did not solve the problem of attack at the carbonyl. When dienone **2.3.16** was exposed to $TiCl_4$ in dichloromethane at -78 ºC, cyclization onto the carbonyl again took place (Equation 2.3.6).



2.3.16 **2.3.17**

Equation 2.3.6 Attempted cyclization of α-cyano dienone

It was reasoned that cyclization into the carbonyl may be occurring because of the proximity of the electron-rich aromatic to the carbonyl (Figure 2.3.1). It was presumed that the conjugate addition of the phenol at the beginning of this route had given a *cis* orientation between the phloroglucinol-derived ring and the carbonyl, and this orientation may be the reason why the electrophilic aromatic substitution onto the carbonyl is the lowest energy pathway.

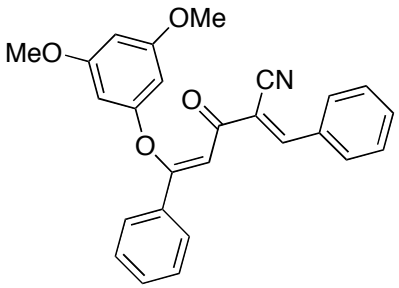
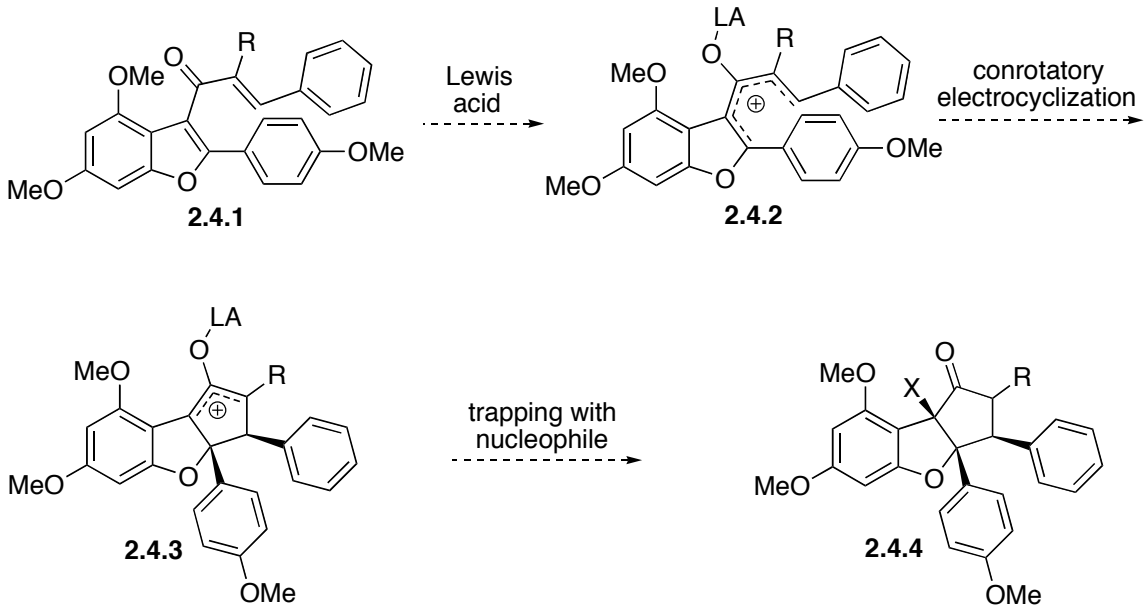


Figure 2.3.1 Possible orientation of aromatic over the carbonyl

The problems associated with the cyclization in this series of dienones were not overcome, so attention turned toward the formation of the benzofuran ring prior to the cyclization event. Incorporation of the benzofuran olefin into the dienone system could avoid the issues faced with the undesired cyclization.

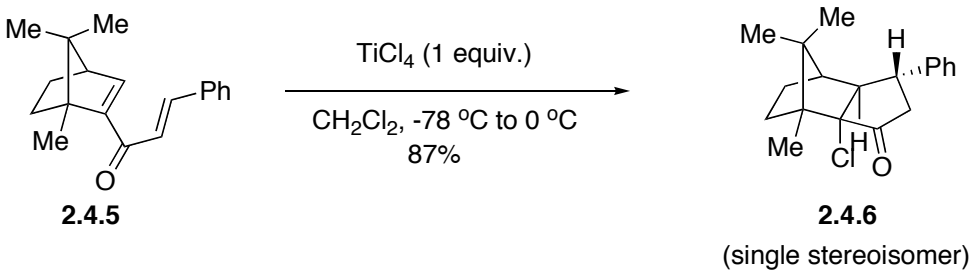
2.4 Benzofuran Dienone Strategy

It was supposed that incorporating the unsaturation of a fully formed benzofuran ring into the dienone system might yield a substrate that could react in a more predictable manner toward a Nazarov cyclization. If an efficient route to a dienone such as **2.4.1** could be found, formation of the C-ring of rocaglamide under Lewis acidic conditions might readily occur (Scheme 2.4.1). Moreover, this strategy could be advantageous since cyclization and trapping of the allylic cation with a nucleophile, such as a halide or water, could install the tertiary benzylic hydroxyl present in rocaglamide.



Scheme 2.4.1 Proposed Nazarov cyclization

Trapping of the Nazarov intermediate with nucleophiles is well documented.[38-44] Of particular interest, was a report by West on halide trapping of the Nazarov intermediates in strained polycyclic systems.[45] He found that treatment of bicyclic dienones such as **2.4.5** with $TiCl_4$ resulted in cyclization and trapping of the intermediate oxoallylic cation by a chloride anion giving **2.4.6** (Scheme 2.4.2). In contrast to the usual elimination pathway, which destroys a stereocenter formed during the electrocyclization, this trapping event preserved both of the newly formed stereocenters. In addition, the process was high yielding and completely stereoselective.



2.4.5 **2.4.6**

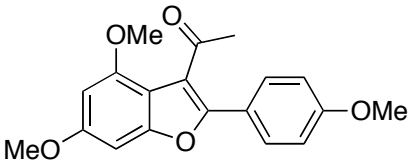
(single stereoisomer)

Scheme 2.4.2 Halide trapping of the Nazarov intermediate

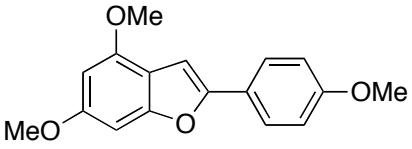
With this in mind, creating routes to the required dienones began the cyclization/nucleophile trapping strategy in relation to the total synthesis of rocaglamide.

2.4.1 Formation of the Benzofuran Ring

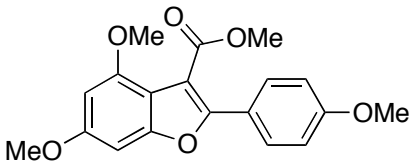
In order to gain access to the dienones that were desired, a good route to the benzofuran ring system was needed. A few different routes were devised that could grant access to various benzofuran ring systems. Synthetic routes to three benzofuran systems in particular were the focus of this work (Figure 2.4.1). It was thought that these scaffolds would provide a good starting point toward the synthesis of a variety of dienones.



2.4.1



2.4.2

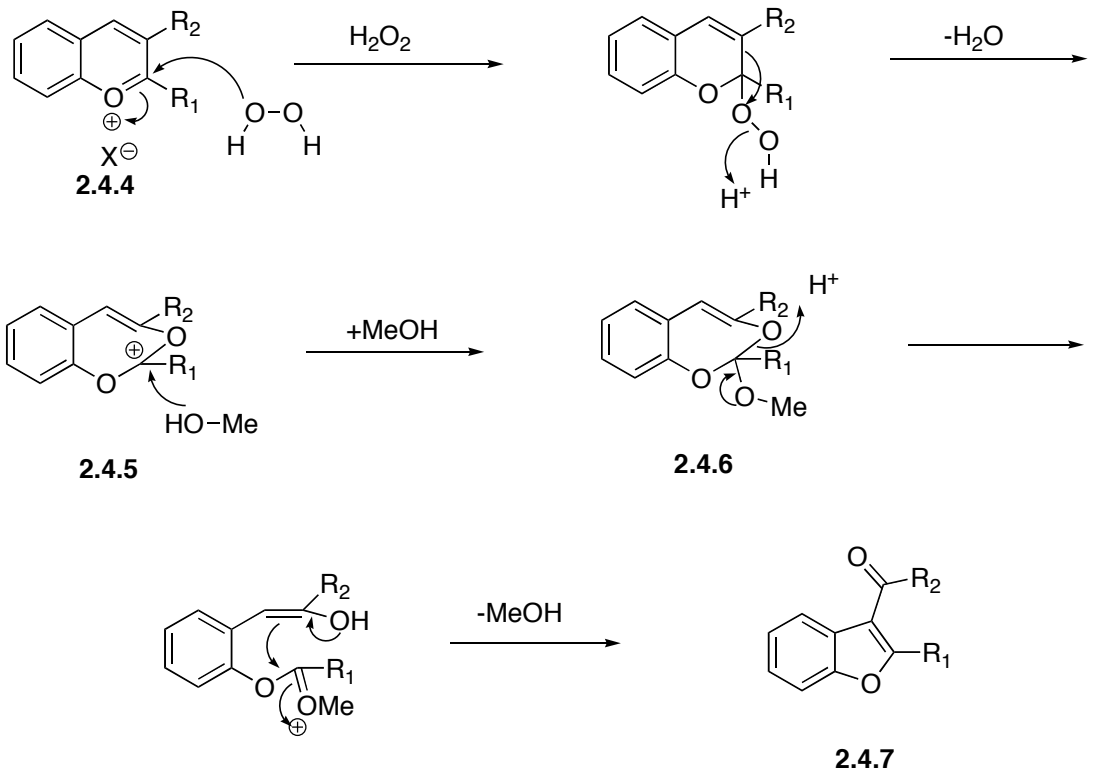


2.4.3

Figure 2.4.1 Desired benzofurans

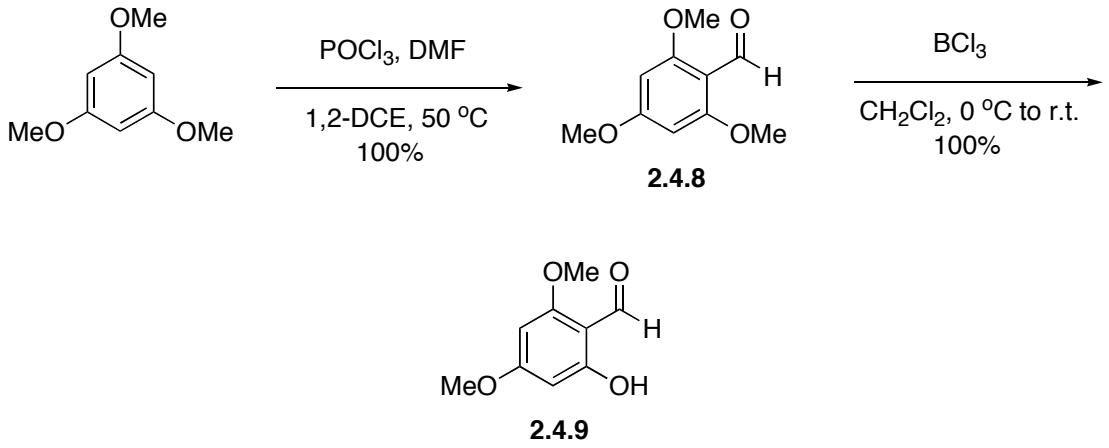
A route to benzofuran **2.4.1,** containing a ketone at the 3-position, was first laid out. This benzofuran could give access to dienones *via* aldol condensation with benzaldehyde.

Published reports for this type of compound relied on a Baeyer-Villiger-type reaction of 3-alkylflavylium salts to form the benzofuran products.[46-48] Mechanistically, the addition of hydrogen peroxide to flavylium salt **2.4.4** is followed by migration of the vinyl group to give carbonium ion **2.4.5** (Scheme 2.4.1). Trapping of the carbonium ion by methanol furnishes compound **2.4.6**. Opening of the 7-membered heterocycle, then closure of the enol onto the oxonium ion and loss of methanol produces benzofuran **2.4.7**.



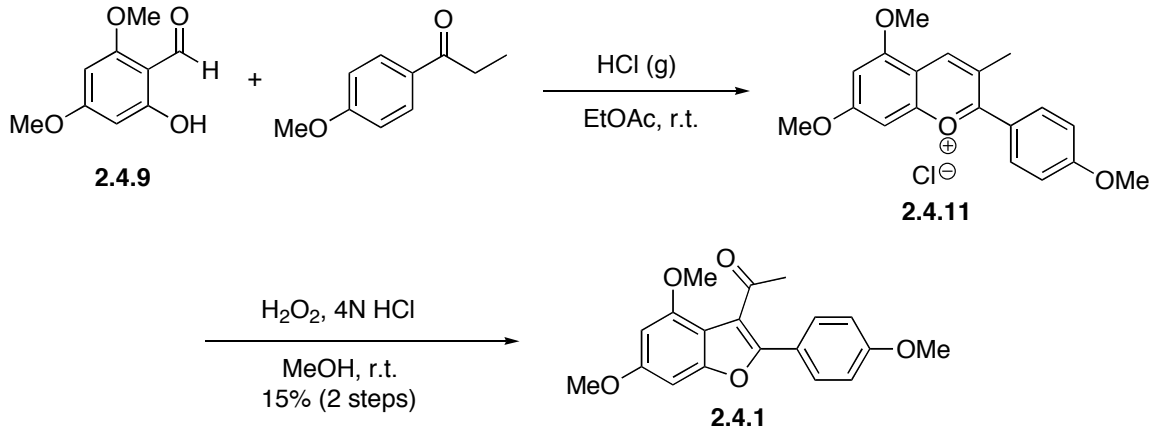
Scheme 2.4.1 Baeyer-Villiger oxidation of 3-alkylflavylium salts

The strategy began with a Vilsmeier-Haack formylation of 1,3,5-trimethoxybenzene to obtain aldehyde **2.4.8** in quantitative yield (Scheme 2.4.2). Demethylation by BCl_3 in CH_2Cl_2 gave phenolic aldehyde **2.4.9**. [49]



Scheme 2.4.2 Formation of phenolic aldehyde for flavylium salt formation

The formation of the benzofuran was accomplished in two more steps. Formation of the flavylium salt **2.4.11** with dry HCl and 4′-methoxypropiophenone in EtOAc, followed by oxidation with hydrogen peroxide in MeOH and 4N HCl gave ketone **2.4.1** in a disappointing 15% yield (Scheme 2.4.3).

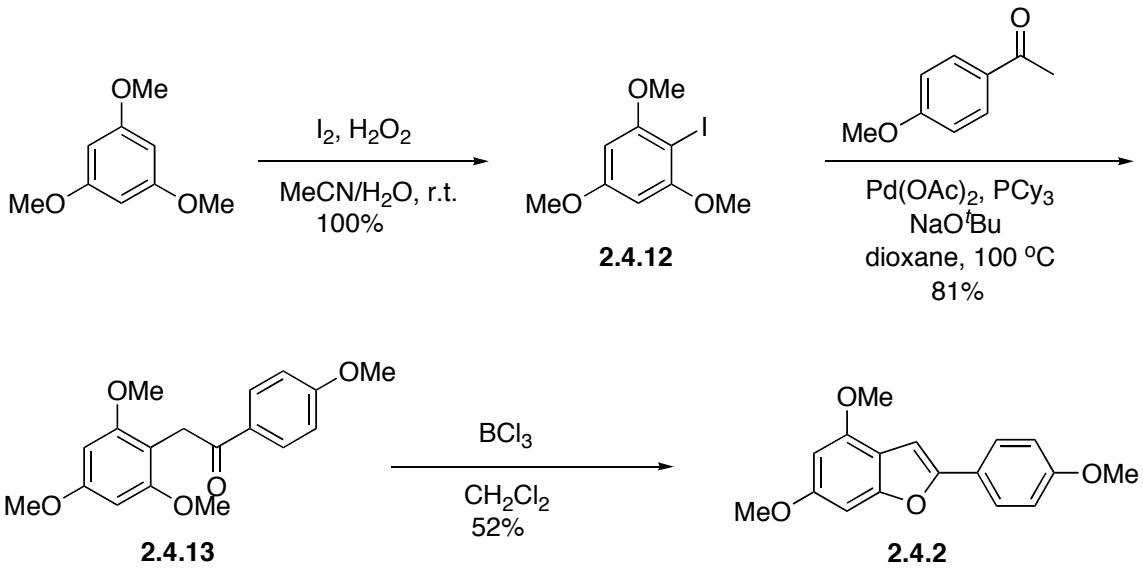


Scheme 2.4.3 Synthesis of benzofuran ketone

A number of conditions were screened for this two-step transformation, but the yield of **2.4.1** could not be improved. Although the desired ketone was available by this route, the low yield associated with the oxidation was not going to be practical for bringing through the large amounts of material needed to advance the synthesis. Therefore, the focus shifted toward making the two other benzofuran substrates.

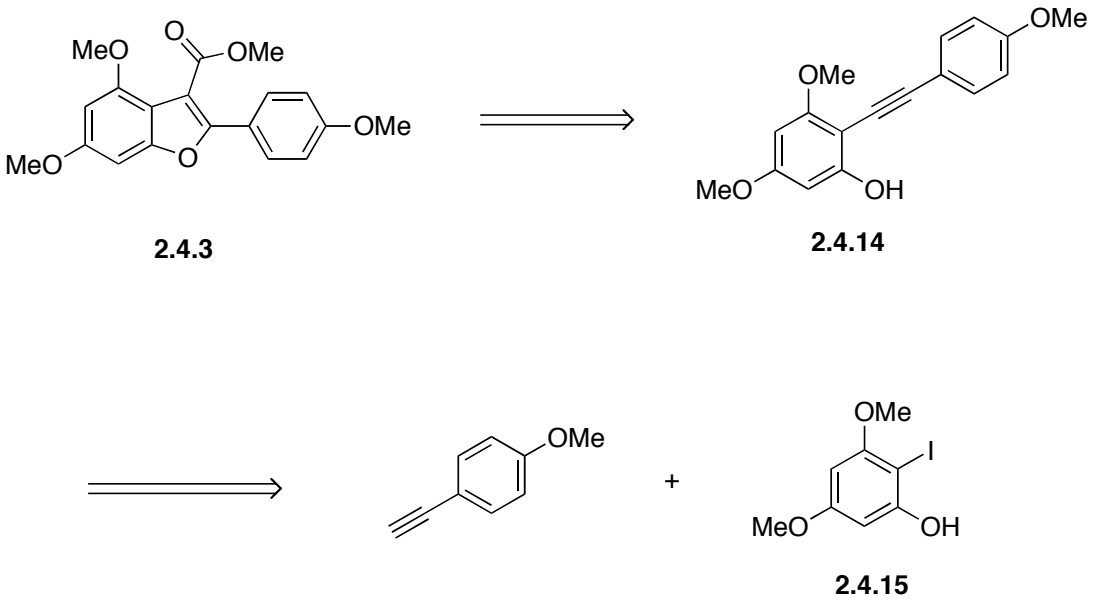
The 3-protio benzofuran **2.4.2** was imagined coming from a Lewis acid promoted demethylation and cyclization. Benzofuran **2.4.2** could grant access to dienones by a Friedel-Crafts acylation at the 3-position of the benzofuran. Alternatively, lithiation of the 3-position followed by acylation could be carried out to obtain the desired dienones.

Benzofuran **2.4.2** was available in 3 steps from 1,3,5-trimethoxybenzene (Scheme 2.4.4.). Iodination of 1,3,5-trimethoxybenzene was carried out with 0.5 equivalents of iodine and hydrogen peroxide to give a quantitative yield of iodinated arene **2.4.12**.[50] Palladium-catalyzed α-arylation[51] of 4′-methoxyacetophenone with iodo-arene **2.4.12** yielded ketone **2.4.13** in 81% yield. The use of tricyclohexylphosphine as the ligand on palladium gave better yields than other phosphine ligands screened (PPh_3, $P(NMe_2)_3$). Comparable yields of **2.4.13** could also be obtained using $Pd(P^tBu_3)_2$ as the source of palladium(0). Finally, formation of benzofuran **2.4.2** proceeded *via* demethylation, cyclization and dehydration using BCl_3 in CH_2Cl_2. This route to benzofuran **2.4.2** was satisfactory since it was short and amenable to scale-up.



Scheme 2.4.4 Formation of 3-protio-benzofuran

Access to the benzo[*b*]furan-3-carboxylate **2.4.3** was also desired. This compound could provide dienones *via* Horner-Wadsworth-Emmons olefination. The ester was imagined coming from a Pd(II)-catalyzed carbonylative cyclization of phenolic acetylene **2.4.14** which, in turn, could be synthesized by Kumada coupling of iodophenol **2.4.15** and 4′-methoxyphenylacetylene (Scheme 2.4.5).[52]

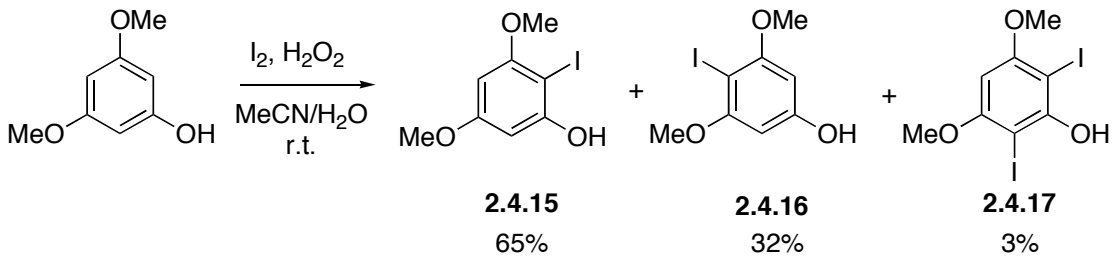


Scheme 2.4.5 Route to benzofuran with methyl ester at 3-position

The synthesis of **2.4.3** began with the iodination of 3,5-dimethoxyphenol. There are many reported procedures for iodination of activated arenes. A protocol was needed that would give a good ratio of *ortho* to *para* iodination and would be scalable, since large amounts of this starting material would be needed.

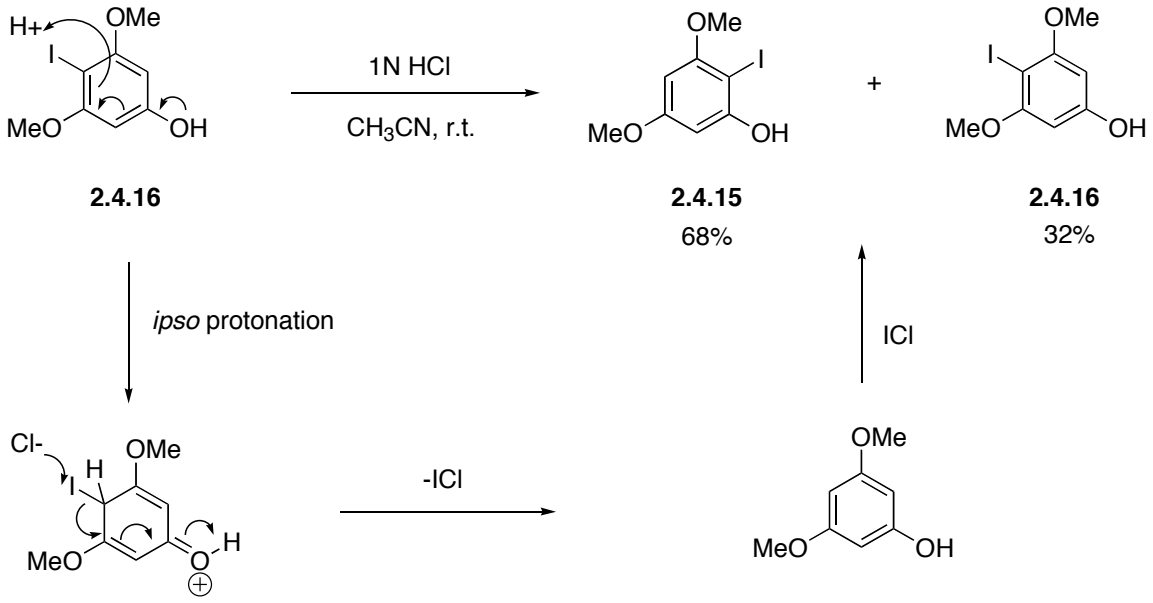
A variety of conditions for the iodination were screened (I_2/$Cu(OAc)_2$,[53] I_2/HgO,[54] I_2/$Fe(NO_3)_3$/$H_3PW_{12}O_{40}$,[55] HIO_4/Al_2O_3,[56] I_2/CAN,[57] I_2/SiO_2/$Fe(NO_3)_3$,[58] I_2/morpholine,[59] NH_4I/Oxone,[60] ICl/$NaHCO_3$[61]). However, they either gave a poor ratio of *ortho* to *para* iodination or significant amounts of diiodination. While the I_2/HgO protocol gave a fair ratio and yield, the results were not always reproducible, and it required a stoichiometric amount of mercury.

Eventually a procedure reported by Stavber *et. al.*[62,63] was used. It required 0.5 equivalents of iodine with 0.65 equivalents of hydrogen peroxide in a mixture of acetonitrile and water (Equation 2.4.1). This procedure gave a 7:3 ratio of *ortho* to *para* iodination in 97% combined yield on scales of up to 50 grams. The two major products could be separated by column chromatography. Small amounts of diiodo compound could be removed by recrystallization from 20% EtOAc in hexanes to yield pure 2-iodo-3,5-dimethoxyphenol **2.4.15**.



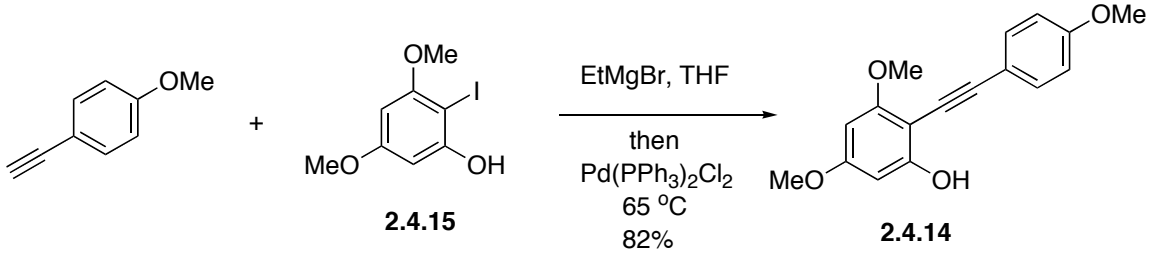
Equation 2.4.1 Iodination of 3,5-dimethoxyphenol

The undesired *para* isomer could also be recycled under acidic conditions to give larger amounts of the *ortho*-iodo compound. Treatment of *para*-iodo compound **2.4.16** with 1N HCl in acetonitrile gave a 7:3 ratio of *ortho*-iodo phenol **2.4.15** to *para*-iodo phenol **2.4.16** (Scheme 2.4.6). This transformation occurs through an *ipso* protonation of **2.4.16**, followed by cleavage of the carbon-iodide bond, giving ICl. The ICl can then iodinate the aromatic ring again, giving the two products. Acetonitrile was necessary as the solvent, because methanol caused the formation the diiodo compound and 3,5-dimethoxyphenol under the same conditions.



Scheme 2.4.6 *Ipso*-protonation/iodination mechanism

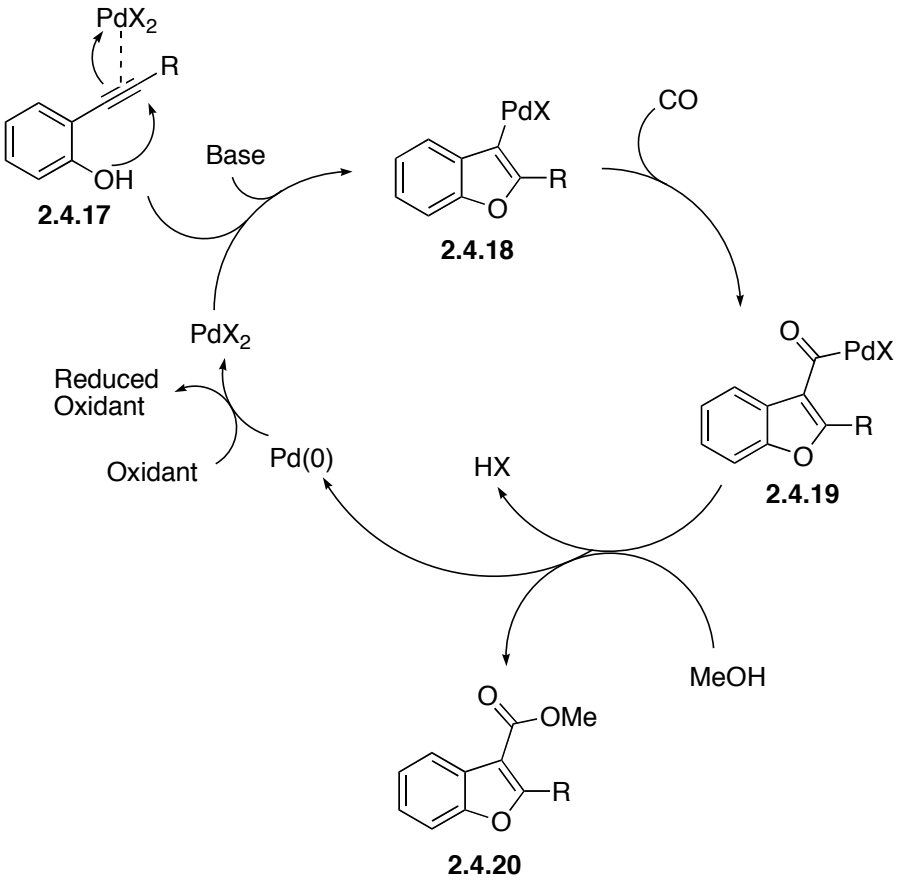
With a reproducible route to significant quantities of iodophenol **2.4.15**, the Kumada[64] cross-coupling, using conditions[52] worked out by Dr. Trevor Rainey, furnished acetylene **2.4.14** in 82% yield (Equation 2.4.2).



Equation 2.4.1 Kumada cross coupling

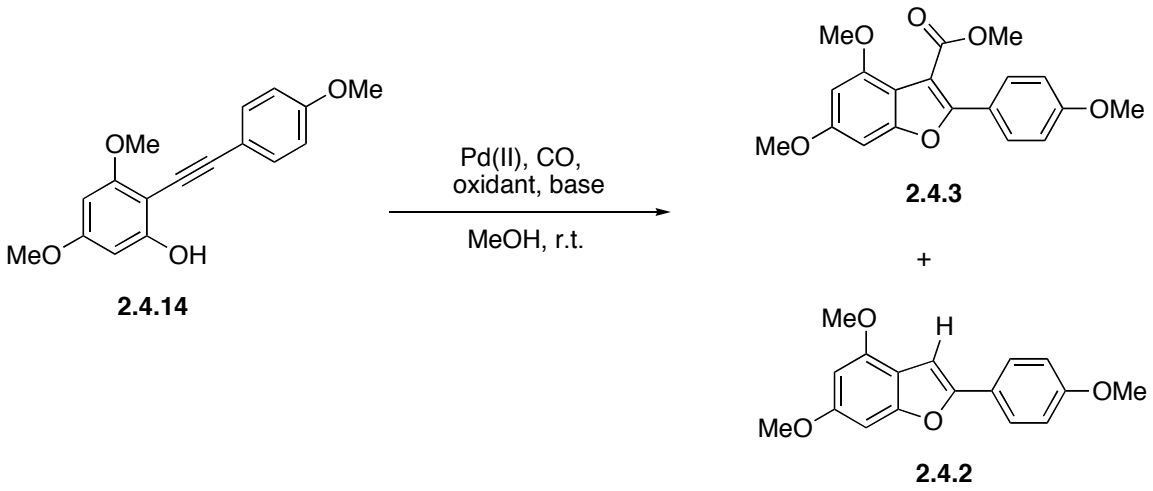
Palladium(II)-catalyzed carbonylative cyclizations are well-precedented.[65-68] Treatment of phenolic acetylenes such as **2.4.14** with a palladium(II) source, a base and an oxidant in an alcoholic solvent under a CO atmosphere gives rise to carbonylated benzofurans.

The mechanism involves coordination of palladium(II) to acetylene **2.4.17** followed by attack of the phenolic oxygen to generate benzofuryl palladium complex **2.4.18** (Scheme 2.4.7). Insertion of carbon monoxide into the carbon-palladium bond generates acylpalladium species **2.4.19**. Attack of methanol on the acylpalladium species followed by reductive elimination with the loss of HX from palladium yields a Pd(0) species and ester **2.4.20**. The Pd(0) is oxidized back to Pd(II) to repeat the cycle.



Scheme 2.4.7 Palladium-catalyzed carbonylative cyclization

A screening of conditions (Table 2.4.1) began for the transformation of **2.4.14** into **2.4.3** (Equation 2.4.2). The 3-protio benzofuran **2.4.2** was isolated as a major by-product in the reaction under a number of conditions tested.



Equation 2.4.2 Palladium-catalyzed carbonylative cyclization

Pd(II) source	**Oxidant**	**Base**	**Yield 2.4.3**	**Yield 2.4.2**
$Pd(OAc)_2$	$CuCl_2$	NaOAc	32%	9%
$Pd(OAc)_2$	$CuCl_2$	K_2CO_3/NaOAc	23%	49%
$Pd(OAc)_2$	CuI/O_2	NaOAc	51%	24%
$Pd(OAc)_2$	CuI/O_2	CsOAc	44%	29%
$Pd(PPh_3)_2Cl_2$	CuI/O_2	K_2CO_3	25%	60%
$PdCl_2$	CBr_4	NaOAc	66%	25%

Table 2.4.1 Conditions for carbonylative cyclization

It was clear from an extensive screening of conditions that cyclization to benzofuran **2.4.2** was problematic. 2-Alkynylphenols such as **2.4.14** are known to autocyclize,[66] and it was observed that if **2.4.14** was not stored in the freezer, it would slowly cyclize to benzofuran **2.4.2**. It was noted that stronger bases, such as potassium

carbonate, gave lower yields of the carbonylated product, and greater quantities of **2.4.2** presumably by cyclization of the phenolate. However, with weaker bases (NaOAc, CsOAc), it was believed that proto-depalladation to **2.4.2** was occurring since acetic acid was being formed in the reaction.

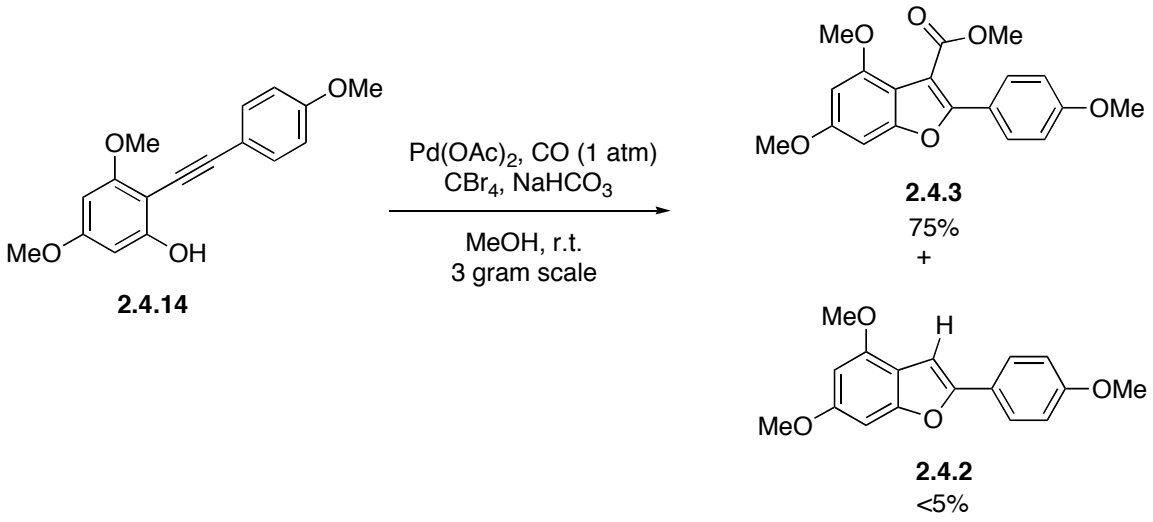
The testing of various oxidants for palladium(0) revealed that carbon tetrabromide was a superior oxidant to any copper source. Carbon tetrabromide was chosen because Yang had previously reported that it functioned well as an oxidant for Pd(0).[68]

The best conditions that could be extracted from the literature were using a system of CBr_4 and NaOAc. However, this procedure only worked well on scales of about 100 milligrams or less. When using scales larger than 100 milligrams, the yield of **2.4.3** dropped dramatically and the 3-protio benzofuran became the major product.

A better procedure to reduce the amount of **2.4.2** formed and increase **2.4.3** was required. It was known at this point that complete deprotonation with a strong base gave a lot of autocyclization, and weaker bases generated acid (AcOH), leading to proto-depalladation. Therefore, it seemed reasonable to try sodium bicarbonate as the base in the reaction. This base would not fully deprotonate the phenol and would only generate water and carbon dioxide upon proton abstraction, thus possibly reducing the formation of **2.4.2**.

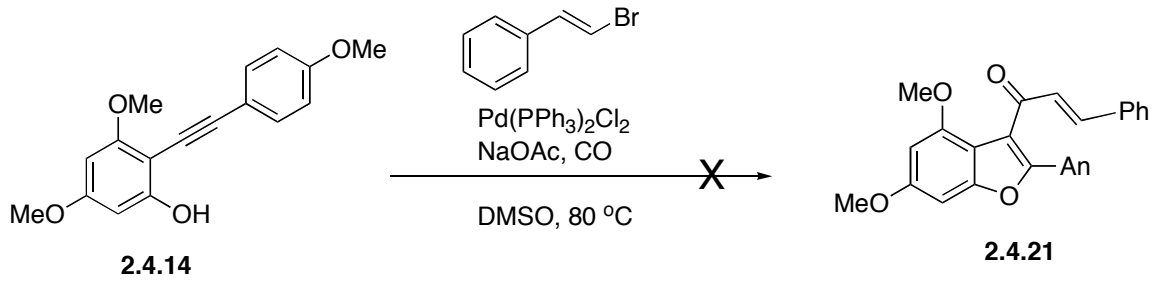
It was exciting to find that the combination of $NaHCO_3$ as the base and CBr_4 as the oxidant provided a 75% yield of the carbonylated product **2.4.3**, with less than 5% of the undesired product **2.4.2** (Equation 2.4.3). This protocol was reproducible on a 3-gram scale. It is also noteworthy that while typical conditions required loadings of 5-10 mol%

palladium, the transformation under these optimized conditions required only 2 mol% palladium. To our knowledge, this is the first time sodium bicarbonate has been employed as the base in this type of transformation.



Equation 2.4.3 Optimized conditions using $NaHCO_3$

Finally, to reduce some steps in the synthesis, a direct conversion of **2.4.14** into dienone **2.4.21** was attempted.[69,70] The transformation employing palladium catalysis, however, was unsuccessful (Equation 2.4.4).



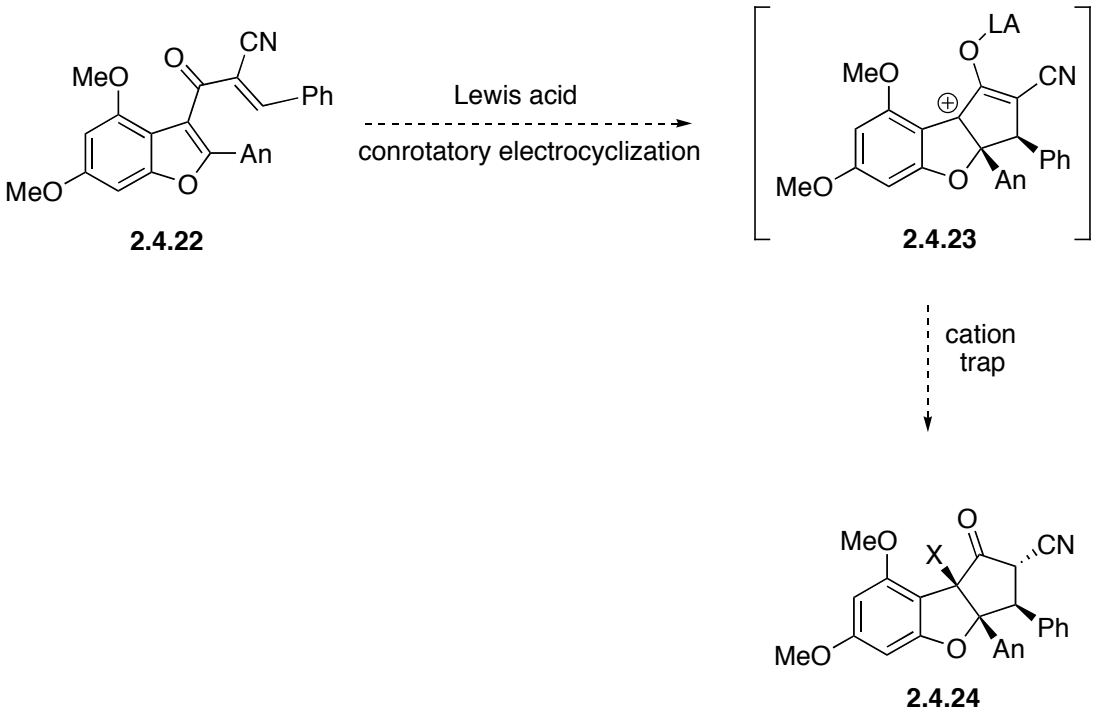
2.4.14 **2.4.21**

Equation 2.4.4 Attempted formation of dienone

With high yielding and scalable routes to two benzofurans, the advancement of these compounds to dienones for the Nazarov cyclization was studied.

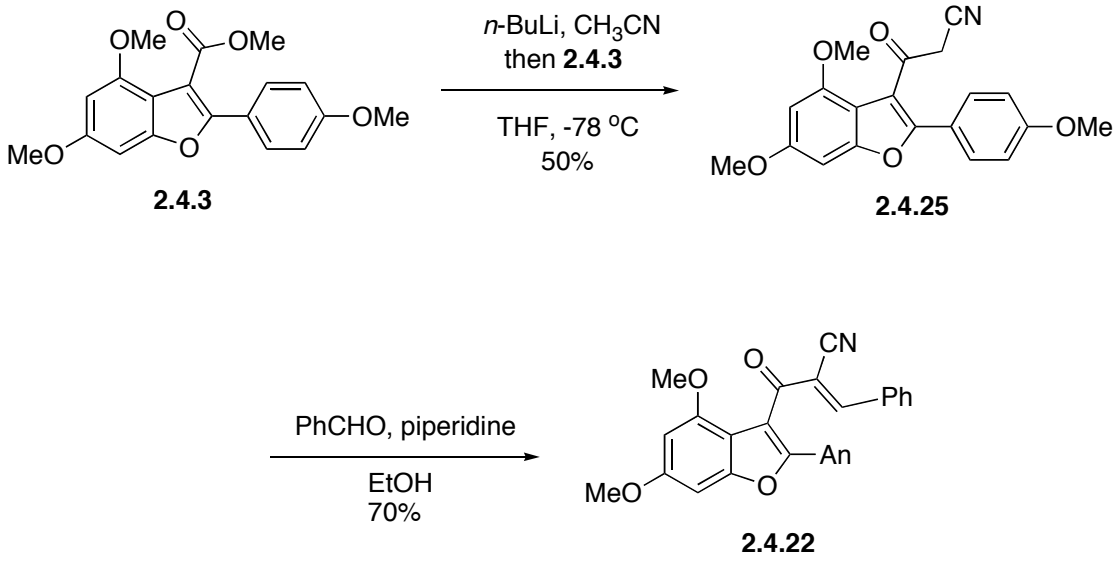
2.4.2 α-Cyano Dienone

Initial studies focused on the cyclization of dienone **2.4.22**, which contains a cyano group at the alpha position. The torquoselectivity of the cyclization should be affected by having the electron-withdrawing group in the α-position, possibly allowing for trapping of the benzylic cation with a nucleophile (Scheme 2.4.8). Nazarov cyclizations of heteroaromatics are known to proceed cleanly when the dienone is polarized.[71,72] However, an interrupted Nazarov reaction occurring with heteroaromatics is unprecedented. If successful, the cyclization of **2.4.22** could provide quick access to rocaglamide.



Scheme 2.4.8 Interrupted Nazarov reaction of α-cyano dienone

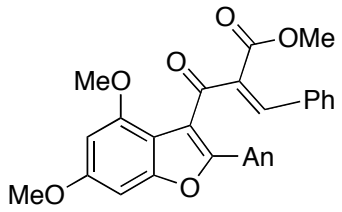
The synthesis of dienone **2.4.22** started with formation of the α-cyano ketone by addition of lithiated acetonitrile to ester **2.4.3** (Scheme 2.4.9). Dienone **2.4.22** was then formed using a Knoevenagel condensation with benzaldehyde. The product was obtained in good yield, and the route provided enough material to test the cyclization.



Scheme 2.4.9 Formation of α-cyano dienone

Dienone **2.4.22** was resistant to cyclization under a variety of conditions. While weak Lewis acids, such as $Cu(OTf)_2$, returned unreacted starting material, harsher conditions only resulted in intractable mixtures. The screening of a number of Lewis acids ($TiCl_4$, $Sc(OTf)_3$, $SnCl_4$, $FeCl_3$) and protic acids (H_2SO_4, HCl), all resulted in decomposition of the starting material.

During the course of our work on the rocaglamides, Alison Frontier at the University of Rochester had been in contact with us about her work on the rocaglamides. Her group had also been working on a synthesis of rocaglamide using a Nazarov strategy. They had synthesized dienone **2.4.27**, a similar substrate to α-cyano dienone **2.4.22**, which they were never able to cyclize (Figure 2.4.2).[73]



2.4.27

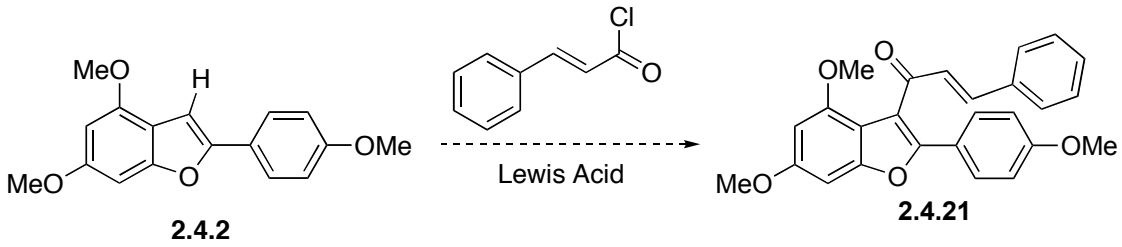
Figure 2.4.2 Frontier's polarized dienone

Since an electron-withdrawing group at the α-position of the dienone was not helping to promote the cyclization, a new approach needed to be taken. In previous work from the Magnus group, Dr. Matt Stent observed that cyclization to the C-ring readily occurred when an electron-donating substituent occupied the 2-position of the pentadienyl cation (see Scheme 1.5.3).[74] This information suggested that the electron-withdrawing group at this position might be hindering the cyclization. Therefore, this α-cyano strategy was discontinued to focus on some substrates that might be better set up for cyclization to the C-ring of rocaglamide.

2.4.3 α-Protio Dienone

Dienone **2.4.21** should be readily accessed from the previously synthesized benzofurans. This compound replaced the electron-withdrawing cyano group with a proton, thus decreasing the polarization of the dienone compared to **2.4.22**. It was thought that this substrate might be better suited for cyclization under Nazarov conditions.

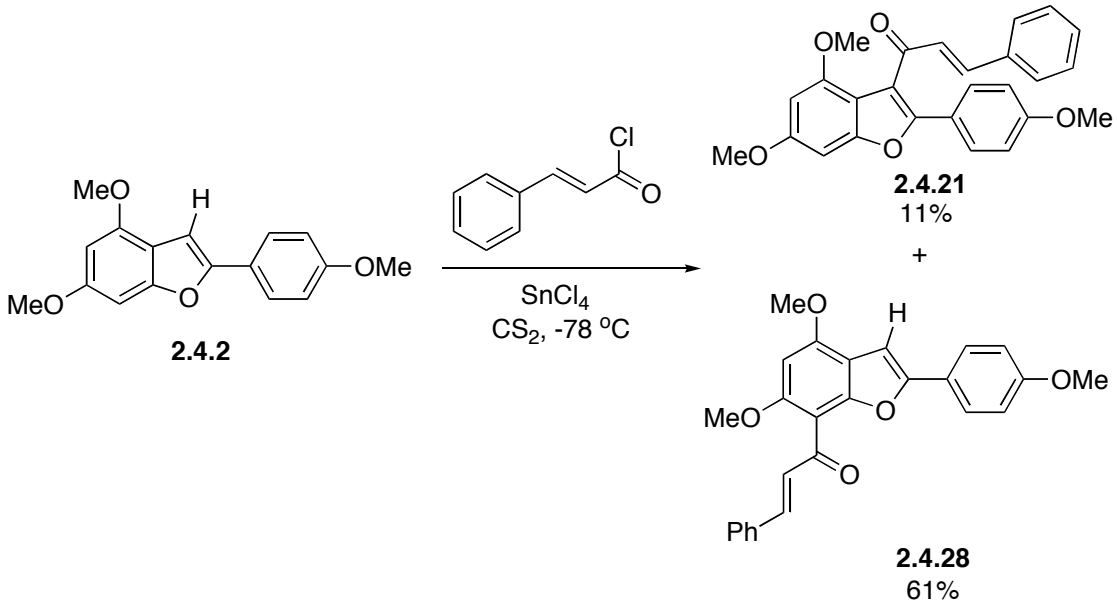
The most direct path to dienone **2.4.21** was *via* Friedel-Crafts acylation of **2.4.2** with cinnamoyl chloride (Equation 2.4.5). Upon treatment of cinnamoyl chloride with a Lewis acid in the presence of benzofuran **2.4.2**, the expectation was that acylation would occur at the 3-position of the benzofuran.



2.4.2 **2.4.21**

Equation 2.4.5 Friedel-Crafts acylation to synthesize α-protio dienone

While dienone **2.4.21** was formed in small amounts using $SnCl_4$ at -78 °C, the major product arose from acylation at C-7 of the benzofuran, yielding **2.4.28** and **2.4.21** in 61% and 11% respectively (Equation 2.4.6).

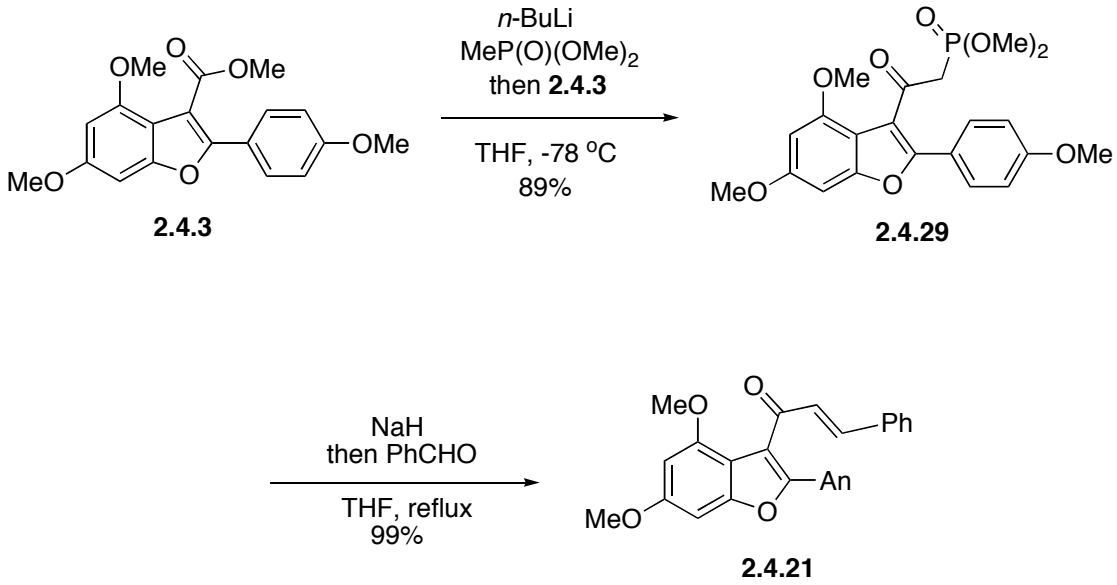


Equation 2.4.6 Friedel-Crafts acylation with cinnamoyl chloride

After extensive screening of solvents (CH_2Cl_2, nitrobenzene, toluene), Lewis acids ($TiCl_4$, $SnCl_4$, $AlCl_3$, $ZnCl_2$) and reaction temperatures, the best ratio of dienone **2.4.21** to C-7 acylated compound **2.4.28** was 1:1.5 using $TiCl_4$ in CH_2Cl_2 at room temperature. More reactive acylium ions, such as that derived from acetyl chloride, only generated the product of acylation at C-7.

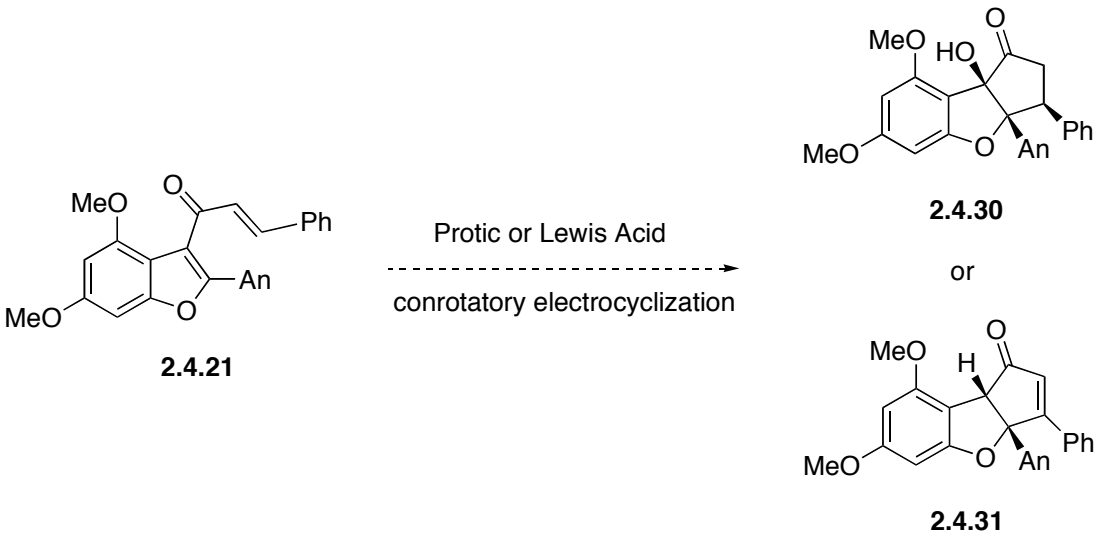
The inclination for electrophiles to react predominantly at the undesired position caused the focus of the research to shift away from the Friedel-Crafts strategy. Lithiation of the benzofuran at the 3-position was also attempted. Upon lithiation of **2.4.2** with LDA or *n*-BuLi, opening of the benzofuran ring occurred to give phenolic acetylene **2.4.14**, and no trapping of electrophiles was obtained. Therefore, a Horner-Wadsworth-Emmons olefination approach to dienone **2.4.21** was used.

Methyl ester **2.4.3** reacted with lithiated dimethyl methylphosphonate providing β-keto phosphonate **2.4.29** in 89% yield (Scheme 2.4.10). Horner-Wadsworth-Emmons olefination with benzaldehyde provided dienone **2.4.21** in excellent yield.



Scheme 2.4.10 Synthesis of α-protio dienone

The Nazarov cyclization of dienone **2.4.21** could now be examined. There were two possible outcomes from the cyclization that were considered (Equation 2.4.7). The first was that cyclization could be followed by trapping of the allylic cation at the benzylic position to obtain cyclopentanone **2.4.30**, an intermediate in Taylor's synthesis of rocaglamide. Secondly, a proton abstraction adjacent to the phenyl could yield cyclopentenone **2.4.31**.



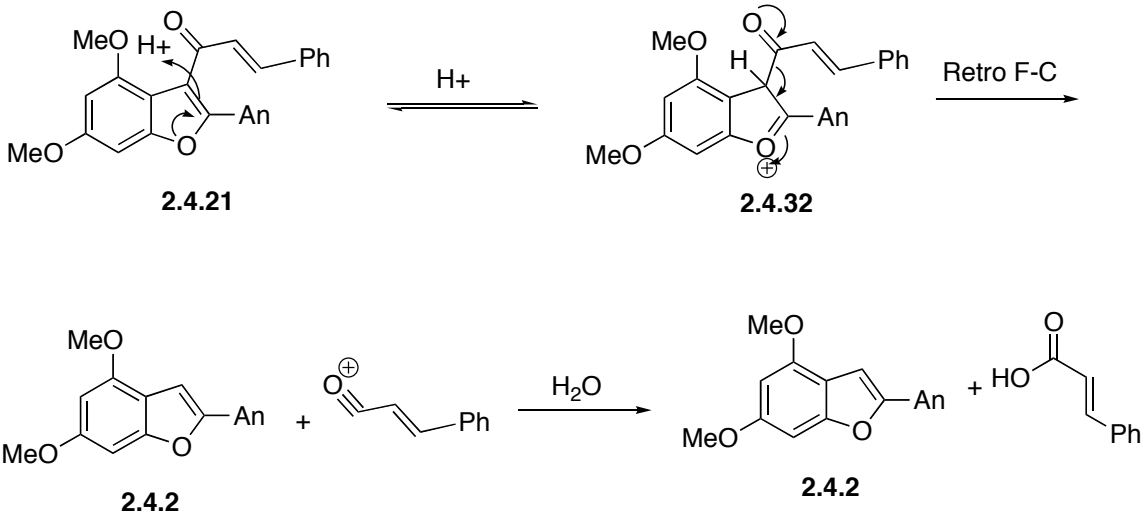
Equation 2.4.7 Desired Nazarov cyclization

The cyclization was attempted under a variety of conditions (Table 2.4.2).[75] Unfortunately, no cyclized products were ever formed. Lewis or protic acids only returned starting material at room temperature, but upon heating the reaction mixtures, a retro Friedel-Crafts reaction would ensue giving the parent benzofuran **2.4.2** and cinnamic acid.

Reagents and Conditions	Results
$AlCl_3$, 1,2-DCE, 50 ºC	Retro Friedel-Crafts
$Cu(OTf)_2$, 1,2-DCE, 120 ºC	No reaction
$Sc(OTf)_3$, 1,2-DCE, 50 ºC	Retro Friedel-Crafts
conc. H_2SO_4, dioxane, 100 ºC	Retro Friedel-Crafts
conc. HCl, dioxane, 100 ºC	No reaction
$TiCl_4$, CH_2Cl_2, r.t.	Demethylation
conc. HCl, AcOH, 100 ºC	Retro Friedel-Crafts

Table 2.4.2 Reaction conditions for Nazarov cyclization

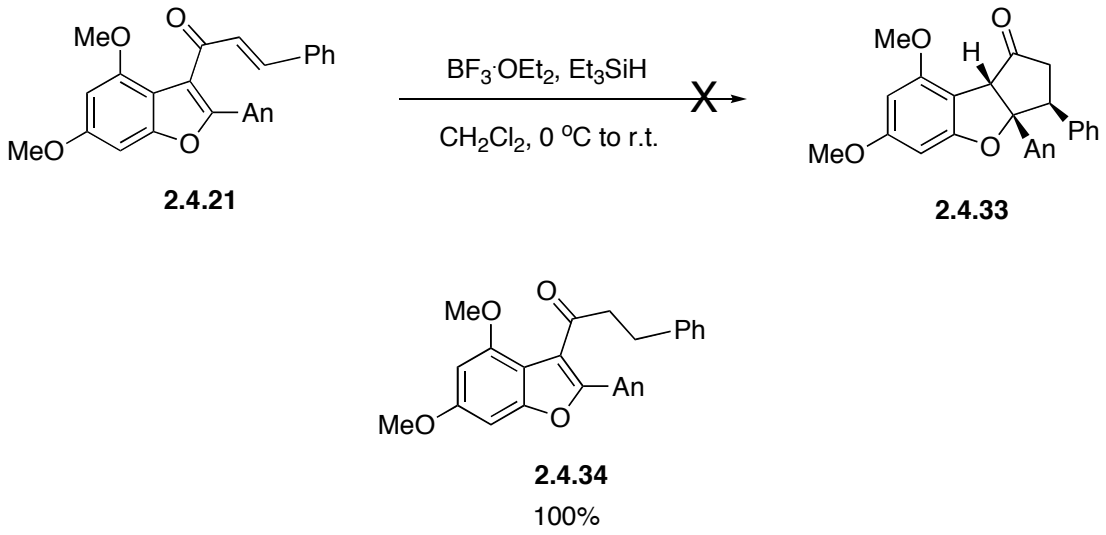
The retro Friedel-Crafts reaction proceeded by protonation of the 3-position of the benzofuran, forming oxonium species **2.4.32** (Scheme 2.4.11). Fragmentation *via* acylium ion formation and quenching of the oxonium ion yields benzofuran **2.4.2** and cinnamic acid upon work-up.



Scheme 2.4.11 The retro Friedel-Crafts fragmentation

It was interesting to observe that concentrated HCl in dioxane at elevated temperatures returned the starting material, as opposed to the retro Friedel-Crafts reaction seen with H_2SO_4 in dioxane and HCl in AcOH. This is important to note, as it will become useful toward understanding future results.

Formation of a delocalized cation was apparent under the reaction conditions since a color change to dark purple would accompany the addition of acid into the reaction mixture. If the cationic cyclization were taking place to a small extent, but just reversing, it might be possible to trap the allylic cation of the cyclized product with an appropriate hydride source. This type of reaction is termed a reductive Nazarov reaction.[76,77] With this in mind, dienone **2.4.21** was treated with BF_3•OEt_2 and triethylsilane in dichloromethane as reported in the literature (Equation 2.4.8). The hope was to isolate cyclopentanone **2.4.33** from the reaction mixture, but a quantitative yield of the reduced enone **2.4.34** was instead obtained.

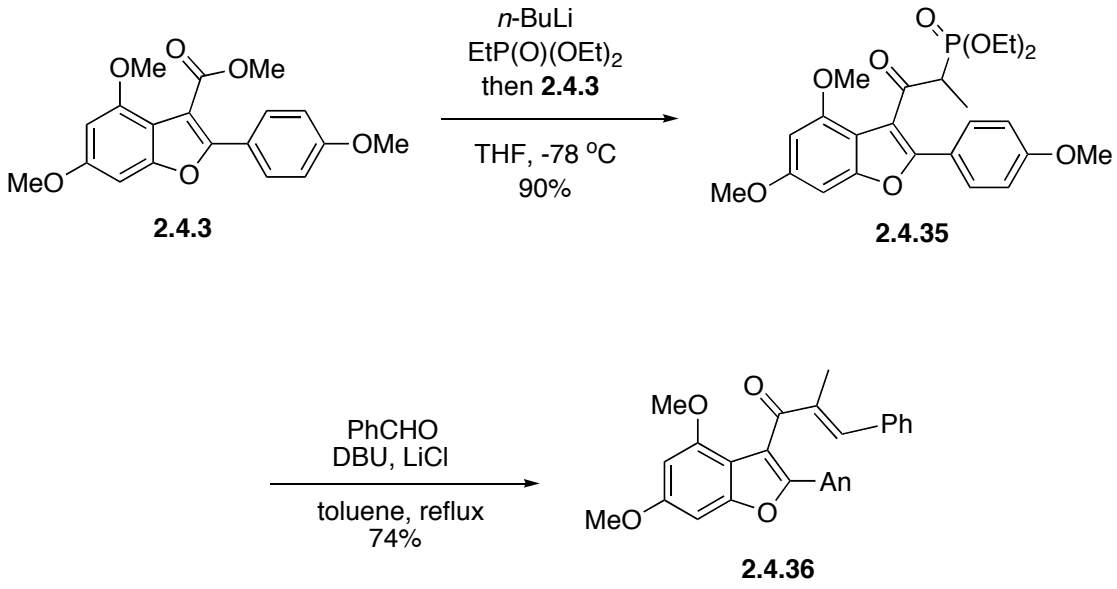


Equation 2.4.8 Attempted Reductive Nazarov

In the case of dienone **2.4.21**, it was believed that the equilibrium of the pentadienyl cation and allylic cation may lie towards the former because of the electron-donating effect of the β-oxygen. Theoretical calculations predict the retro Nazarov reaction to be highly exothermic when an alkoxy group occupies the β-position of the dienone, and experiments support this prediction.[78,79] Thus, it was hypothesized that by providing increased stabilization of the allylic cation through more substitution at the α-position, the cyclization may occur more readily. Trapping of the allylic cation or proton loss to an alkene would drive the reaction to completion by providing a thermodynamic sink. The feasibility of this hypothesis could be tested by incorporation of a methyl substituent at the α-position of the dienone.

2.4.4 α-Methyl Dienone

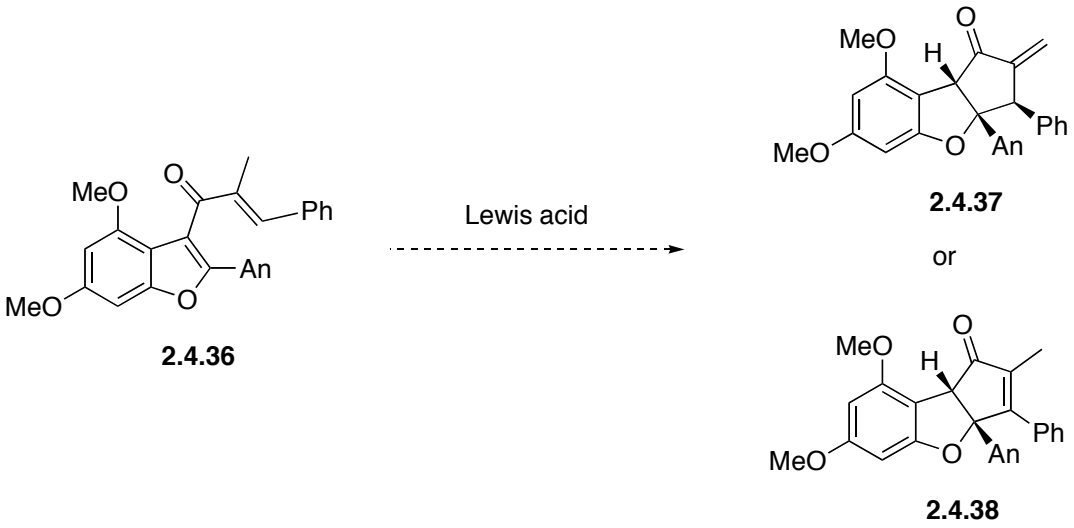
The synthesis of the α-methyl dienone proceeded by reaction of ester **2.4.3** with lithiated diethyl ethylphosphonate to give β-ketophosphonate **2.4.35** (Scheme 2.4.12). Horner-Wadsworth-Emmons olefination using Masamune-Roush conditions[80] yielded dienone **2.4.36** in 74% along with recovered starting material.



Scheme 2.4.12 Formation of α-methyl dienone

Nazarov cyclizations leading to α-methylenecyclopentanones are known,[81,82] and it was possible that treatment of **2.4.36** with a Lewis acid could trigger the cyclization and loss of a proton to **2.437** (Equation 2.4.9). If **2.4.37** were obtained, the oxidation of the exo-methylene and advancement of this compound to rocaglamide should be straightforward. There was also the possibility that proton loss may take place next to the

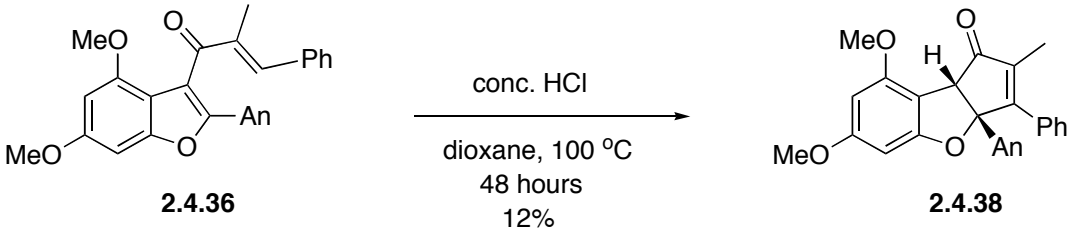
phenyl substituent yielding **2.4.38**, but proton loss from the methyl would statistically be more probable.

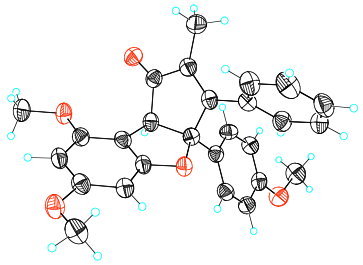


Equation 2.4.9 Nazarov cyclization of **2.4.36**

The screening of conditions began to determine if the incorporation of a methyl at the α-position of the dienone would increase the propensity toward cyclization. Heating **2.4.36** with a variety of Lewis acids ($SnCl_4$, $AlCl_3$, $Sc(OTf)_3$, etc.) only caused fragmentation of the molecule in a retro Friedel-Crafts fashion. This was disappointing, as this problem had been encountered with the α-protio dienone as well. However, upon treatment with concentrated HCl in dioxane at 100 °C for 48 hours,[83] a new compound had formed. Upon purification of the reaction mixture, cyclopentenone **2.4.38** was isolated in 12% yield, along with a large amount of unreacted and decomposed materials (Equation 2.4.10). The structure of **2.4.38** was confirmed by X-ray crystallography (See

Appendix 2). This result proved our hypothesis that adding a methyl substituent at the α-position of the dienone would increase the reactivity.





Equation 2.4.10 Successful cyclization

The double bond ended up endocyclic meaning that the C-3 stereocenter formed during the cyclization was destroyed. Though not ideal, this result should not be problematic since Trost had reported a selective reduction of a cyclopentenone to the *cis* diaryl configuration in his synthesis of rocaglamide. We were also confident that oxidation of the methyl to the dimethyl amide could be achieved on this substrate by allylic oxidation. Therefore, optimization of the reaction conditions was investigated to improve the yield and decrease the reaction time.

The crude reaction mixture had a lot of decomposed material in the NMR spectrum. It was believed that this decomposition might have resulted from two possible

reactions. First, some could arise from the opening of dioxane by HCl under the reaction conditions. Also, once the product **2.4.38** was observed by TLC, the reaction mixture turned a dark crimson color. This color change may have been indicative of the opening of the furan ring to form a triarylcyclone (Figure 2.4.3). Triarylcyclones are known to turn a solution dark crimson and they are quite reactive.[84] It was believed that this triarylcyclone might be decomposing under the strongly acidic conditions. These side reactions needed to be avoided in order to improve the yield and decrease the reaction time for this transformation.

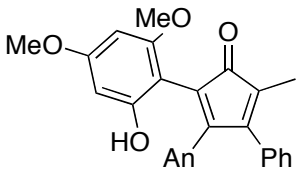


Figure 2.4.3 Triarylcyclone

It was thought that using milder conditions to induce the cyclization could lessen the side reactions. Therefore, the dienone was treated with a more dilute solution of HCl (6M) in dioxane. However, this made the reaction proceed even slower and did not improve the yield.

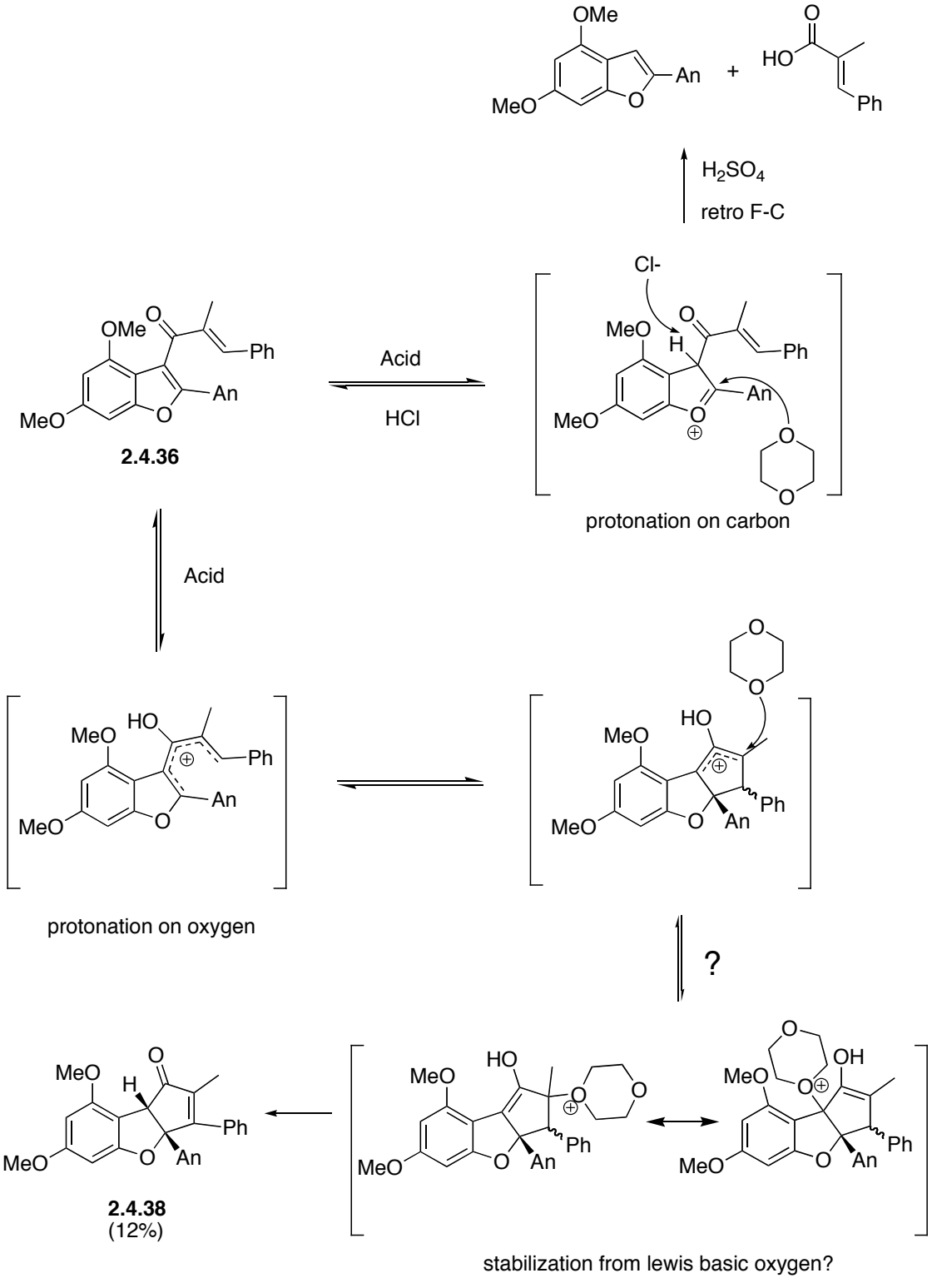
Other conditions employing concentrated HCl were examined to improve the efficiency of the reaction. When acetic acid was used as the solvent, a small amount of cyclopentenone **2.4.38** was produced, but the major product arose from a retro Friedel-

Crafts reaction. Running the reaction in 1,2-DCE only caused the retro Friedel-Crafts fragmentation.

Interestingly, the use of varying concentrations of H_2SO_4 in dioxane only gave the fragmentation products of the parent benzofuran and α-methylcinnamic acid.

This led to the supposition that the chloride counterion from HCl might have been playing a role in promoting the cyclization, possibly by trapping the allylic cation intermediate and subsequently getting eliminated. Thus, it was reasoned that adding chloride to the reaction mixture might be beneficial. The addition of 5-10 equivalents of LiCl to the mixture of conc. HCl in dioxane, however, did nothing to shorten the reaction time or improve the yield.

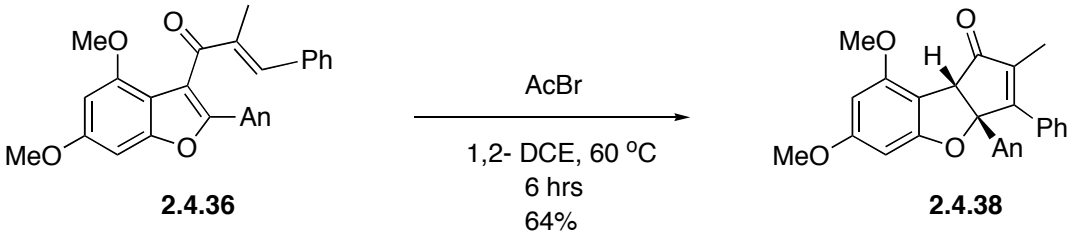
At this point, a deeper understanding about what was occurring in this reaction was needed. The known facts were that the best results came using conc. HCl in dioxane as solvent. Other solvents and acids were not as efficient or caused the fragmentation to take place. We hypothesized that dioxane, being a participating solvent, may be playing a role in stabilizing some of the intermediates involved in the cyclization. Furthermore, the chloride counterion may be necessary to prevent the retro Friedel-Crafts reaction by making the protonation at C-3 of the benzofuran reversible (Scheme 2.4.13). This hypothesis might also support why no reaction was observed in the case of the α-protio dienone, since dioxane could stabilize the oxonium species formed upon carbonyl protonation and the chloride counterion prevented the retro Friedel-Crafts from occurring when protonation occurred at C-3 of the benzofuran.



Scheme 2.4.13 Nazarov cyclization hypothesis

The hypothesis that dioxane was providing intermolecular stabilization of the Nazarov intermediates led the idea of using intramolecular stabilization of the oxyallyl intermediate to further improve the effectiveness of the cyclization. Consequently, acylation of the carbonyl as a means of inducing the cyclization was explored. Although Ac_2O had been screened in the past with no positive results,[52] it was believed that a more reactive acylating agent might be necessary to achieve the cyclization.

Acetyl bromide was chosen as the acylating reagent since it is very reactive and contains a good leaving group in Br-. It was assumed that a more stable leaving group would make the acylation of the carbonyl less reversible. This notion was proven correct when, upon treatment with AcBr in 1,2-DCE at 60 ºC for 6 hours, cyclopentenone **2.4.38** was isolated in 64% yield (Equation 2.4.11). Not only did these conditions improve the yield 5-fold, but they also significantly reduced the reaction time and lowered the energy required for cyclization.

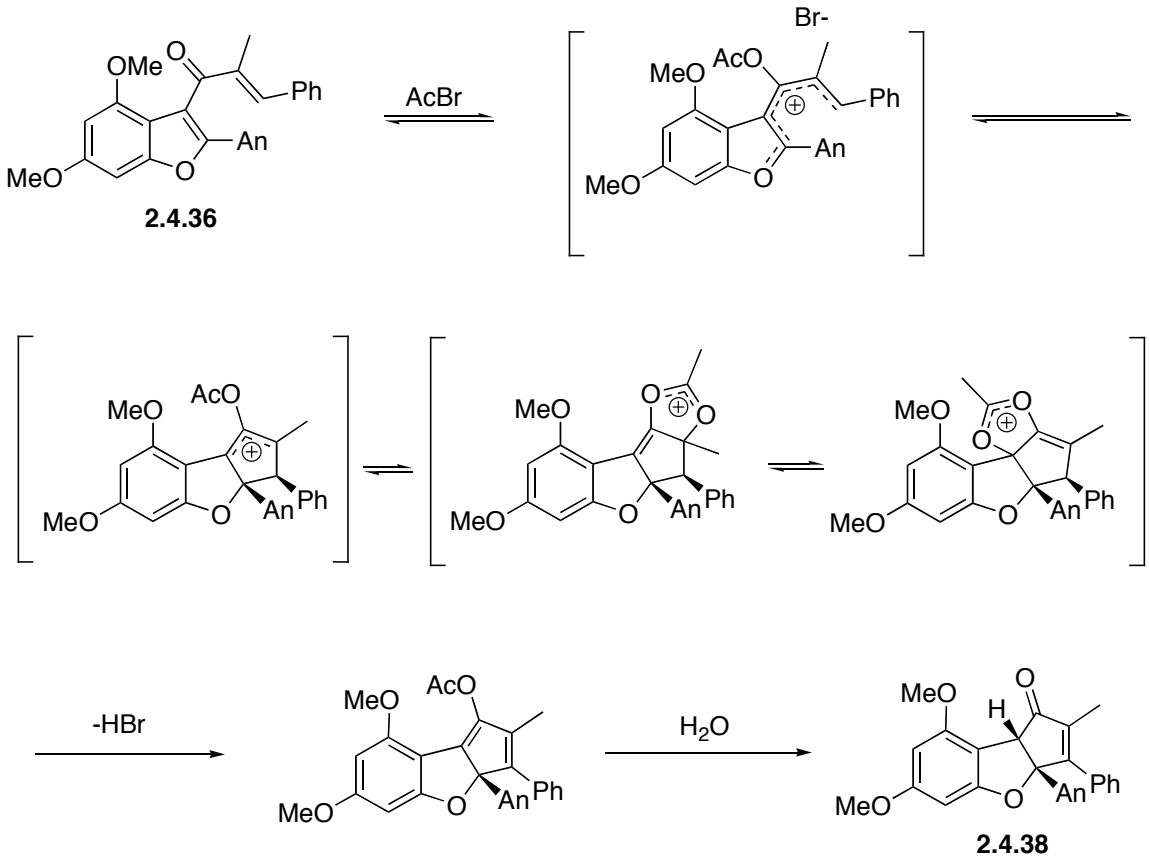


Equation 2.4.11 Nazarov cyclization using acetyl bromide

Acetyl chloride was also tested for the cyclization. However, only starting material was recovered after heating to 150 ºC in a sealed tube. This result was

rationalized by comparing the relative stabilities of the leaving groups. Since bromide is a more stable leaving group than chloride, it was believed that the use of an acid bromide renders the acylation less reversible than with acid chlorides.[85] To the best of our knowledge, this is the first time an acid bromide has been used to initiate a Nazarov cyclization.

Based on these results, it was proposed that the reaction proceeded by acylation of the carbonyl followed by cyclization to the allylic cation (Scheme 2.4.14). Stabilization of the cation by neighboring group participation of the acetate followed by proton loss gave the enol acetate. Proton loss could either occur from the methyl, forming the exo-methylene, which isomerized to the internal alkene with acid, or by direct loss of the proton adjacent to the phenyl. Hydrolysis of the enol acetate on aqueous work-up provided cyclopentenone **2.4.38**.



Scheme 2.4.14 Mechanism of cyclization by acylation

Even though this cyclization has been referred to as a Nazarov cyclization, there is no way of determining if it was indeed a stereospecific conrotatory electrocyclization since the stereochemistry at C-3 was lost. It was possible that the reaction may have been either a cationic Prins-type cyclization or a Nazarov cyclization. Either way, a good yield of **2.4.38** was obtained and the advancement toward rocaglamide could be continued.

The installation of the benzylic hydroxyl and oxidation of the methyl group to a dimethyl amide needed to be addressed to complete the total synthesis. The allylic oxidation of the methyl substituent was examined first.

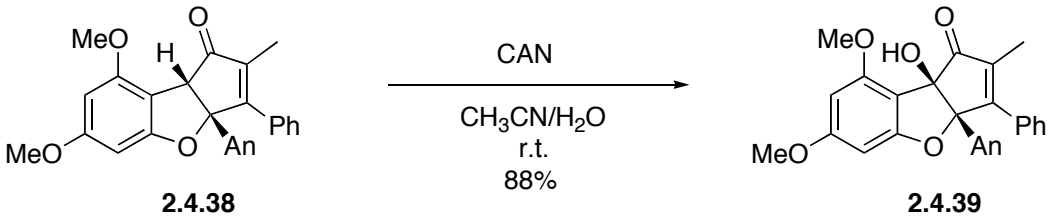
Many conditions were screened to oxidize the methyl group, but no methyl oxidation products were ever observed (Table 2.4.3). Selenium dioxide and Pd(II) oxidations[86] returned starting material. Chromium trioxide/3,5-dimethylpyrazole[87] and DDQ destroyed the molecule, while allylic bromination conditions resulted in multiple halogenations of the aromatics. It was surprising that singlet oxygen gave no reaction as Foote had previously reported the oxidation of exo-methyl groups on cyclopentenones using those conditions.[88]

Reagents and Conditions	**Results**
SeO_2, dioxane or DCE, heat	No reaction
SeO_2/*t*-BuOOH, DCE, heat	No reaction
Pd(II)/*t*-BuOOH, DCE, heat	No reaction
CrO_3/3,5-dimethylpyrazole, CH_2Cl_2, 0 ºC	Decomposition
DDQ, CH_2Cl_2, r.t.	Intractable mixture
NBS, benzoyl peroxide or AIBN, CCl_4, reflux	Aromatic halogenation
$^1O_2$, various sensitizers	No reaction

Table 2.4.3 Some allylic oxidation conditions screened

The installation of the tertiary hydroxyl was also being examined. Ammonium cerium(IV) nitrate (CAN) in a 1:1 mixture of acetonitrile and water was found to selectively oxidize the benzylic position in excellent yield (Equation 2.4.12).[89] This

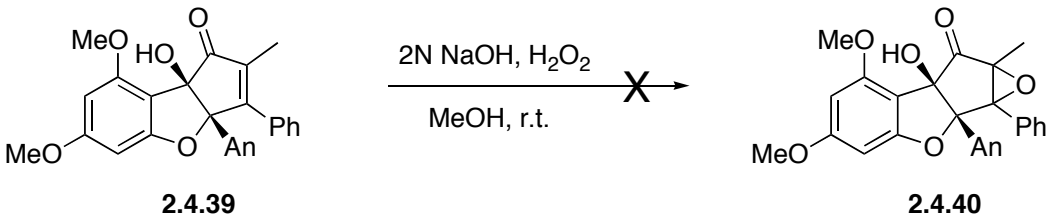
compound was also confirmed by X-ray crystallography (See Appendix 3), since the phenyl group strangely came as a singlet in the ^{1}H NMR spectrum. It was remarkable that oxidation of the benzylic position took precedent over oxidation of the extremely electron-rich aromatic to the quinone.[90]



2.4.38 **2.4.39**

Equation 2.4.12 Oxidation of the benzylic position

With the benzylic hydroxyl in place, oxidation of the methyl was again investigated. Sadly, none of the conditions screened, including those in Table 2.4.3, gave any of the desired oxidation product. A less direct route to the oxidation though epoxide opening was envisioned as well, but attempts at epoxidizing the enone under basic conditions only returned starting material (Equation 2.4.13).

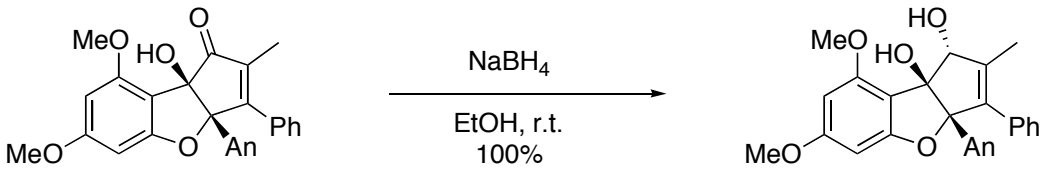


2.4.39 **2.4.40**

Equation 2.4.13 Epoxidation of the enone

Since the oxidation of the methyl had proven to be more difficult than anticipated, we decided to reduce the ketone to the *trans* diol, as this is the required stereochemistry for rocaglamide. Additionally, the reduction should render the double bond more electron-rich, making it more reactive toward allylic oxidation.

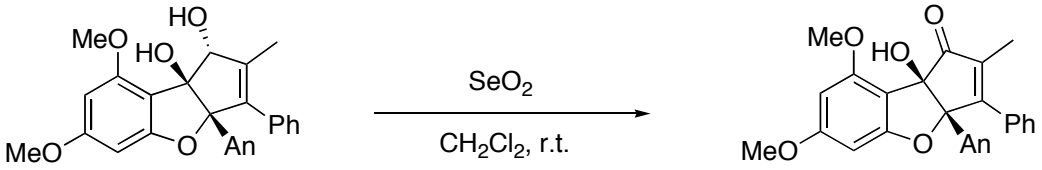
While reduction with DIBAL or LAH gave mixtures of *cis* and *trans* diols, $NaBH_4$ gave a quantitative yield of the *trans* diol **2.4.41** (Equation 2.4.14). The stereochemistry was determined by X-ray crystallography (See Appendix 4). The reduction most likely proceeded by templation of the $NaBH_4$ to the tertiary alcohol followed by delivery of a hydride from the same face, to give exclusively the *trans* diol.



2.4.39 **2.4.41**

Equation 2.4.14 Reduction to *trans* diol

When the diol was treated with SeO_2 in dichloromethane, the hope was that oxidation of the methyl substituent would take place. The oxidation, however, occurred internally and ketone **2.4.39** was returned (Equation 2.4.15). Singlet oxygen also gave similar results.

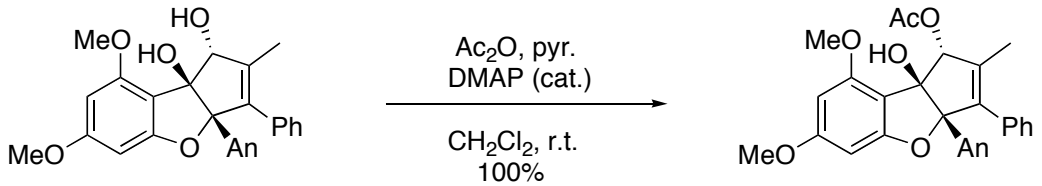


2.4.41 **2.4.39**

Equation 2.4.15 Oxidation of *trans* diol

It was reasoned that oxidation of the methyl over the internal oxidation could be obtained if the secondary alcohol were transformed into an acetate. The acylation should change the electronics of the system by pulling electron density from the internal hydrogen, thus making it less labile. In turn, this might bias the oxidation unto the external methyl.

Treatment of diol **2.4.41** with acetic anhydride and catalytic DMAP gave the secondary acetate **2.4.42** in quantitative yield (Equation 2.4.16). Again, all efforts to oxidize the methyl of **2.4.42** using standard allylic oxidation conditions failed.



2.4.41 **2.4.42**

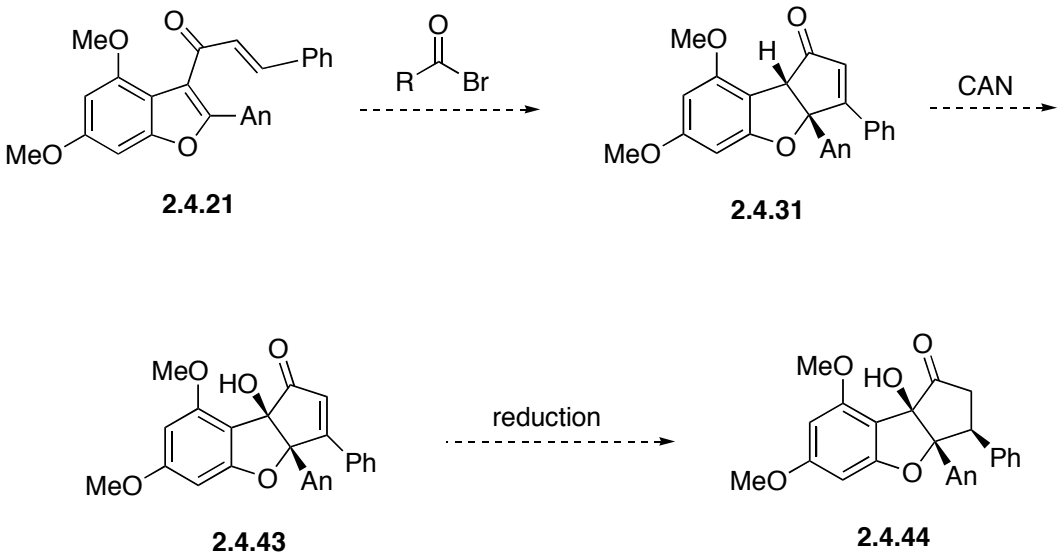
Equation 2.4.16 Formation of acetate

The inability to oxidize the exo-methyl after the successful cyclization was disappointing. However, since acetyl bromide was found to promote the cyclization of

the α-methyl dienone **2.4.36**, it was crucial to try these new reactions conditions on the α-protio compound **2.4.21**. If the cyclization were to be successful with **2.4.21**, the troublesome oxidation of the methyl substituent could be avoided. Therefore, the α-protio dienone was revisited.

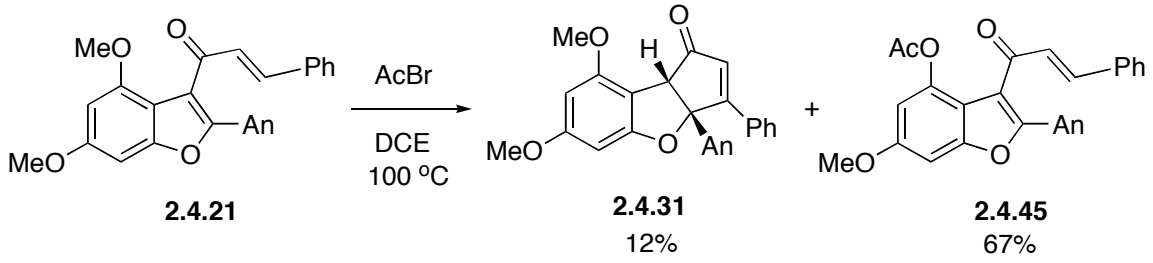
2.4.5 Revisiting the α-Protio Dienone

The cyclization of **2.4.21** was envisioned taking place under similar conditions as the α-methyl dienone to give cyclopentenone **2.4.31** (Scheme 2.4.15). Benzylic oxidation could then be achieved using CAN, as this had worked well on the previous substrate. Reduction of the double bond could give **2.4.44**, an intermediate in Taylor's synthesis of rocaglamide.



Scheme 2.4.15 Proposed route to Taylor's intermediate

Treatment of dienone **2.4.21** with AcBr in 1,2-DCE at 60 °C, the conditions used to cyclize the α-methyl dienone, gave no reaction. However, once the temperature was increased to 100 °C, the starting material was consumed and two products were isolated (Equation 2.4.17). Cyclopentenone **2.4.31** was produced in 12% yield along with dienone **2.4.45**, a product derived from a demethylation and acylation of one of the methoxyls on the A-ring.



2.4.21

2.4.31
12%

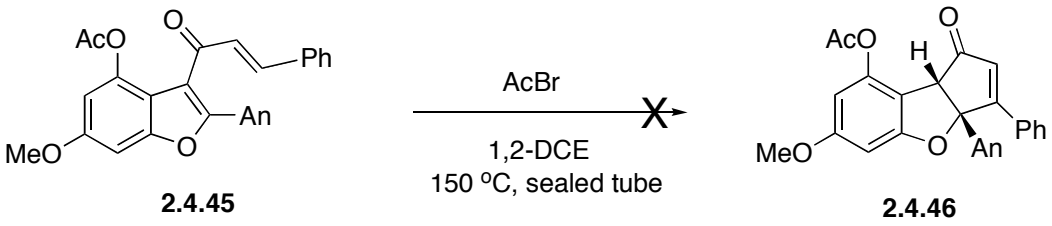
2.4.45
67%

Equation 2.4.17 Cyclization of α-protio dienone

It was apparent that the HBr generated during the course of the reaction was causing the demethylation to occur. HBr is a classical reagent for demethylation of aromatic methoxyls. The demethylated/acylated product's structure was assigned as **2.4.45** for it was assumed that a proton transfer occurred from the carbonyl to the nearest methoxyl on the A-ring to cause the demethylation.

The formation of **2.4.45** was not seen as problematic if the cyclization of this compound could still be induced. If the cyclization of **2.4.45** happened, the product **2.4.46** could be deacylated and remethylated to give **2.4.31**. However, treatment of

2.4.45 with acetyl bromide in a sealed tube up to 150 °C only returned starting material (Equation 2.4.18).



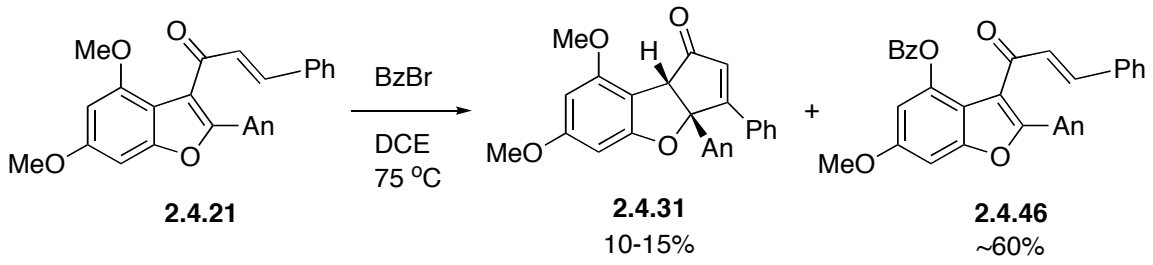
2.4.45 **2.4.46**

Equation 2.4.18 Failed cyclization of **2.4.45**

This result implied that an extremely electron-rich A-ring might be necessary for stabilization of the allylic cation formed upon cyclization, since the phenolic acetate **2.4.45** would not cyclize. It also suggested that demethylation of the aromatic methoxyls by HBr would need to be prevented in order to improve the reaction.

Since no demethylation was observed in the α-methyl series at the 60 °C required for cyclization, it was believed that it might be possible to prevent the demethylation by lowering the temperature required for the cyclization of α-protio compound **2.4.21**. One way to do that could involve the use of an acid bromide capable of stabilizing the cationic intermediates to a greater extent. Therefore, benzoyl bromide was studied for the cyclization, as the benzene ring should stabilize a cation to a greater extent than the methyl of acetyl bromide.

The cyclization did indeed occur at a lower bath temperature of 75 °C with benzoyl bromide, but demethylation was still a problem (Equation 2.4.19).

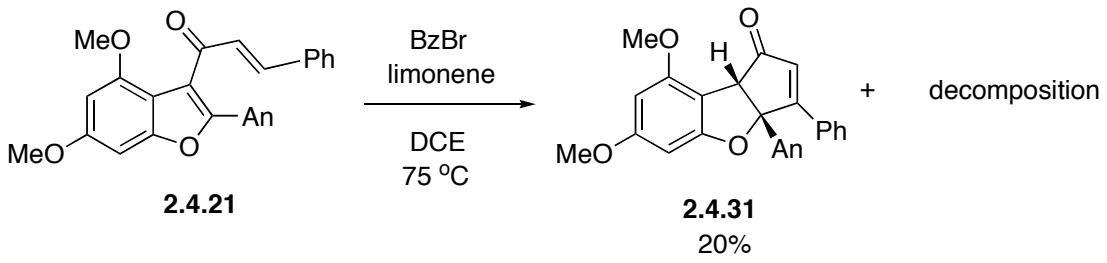


2.4.21 **2.4.31** 10-15% **2.4.46** ~60%

Equation 2.4.19 Cyclization using benzoyl bromide

To avoid the demethylation, HBr needed to be destroyed as it was formed in the reaction. Inorganic bases. such as K_2CO_3 or Al_2O_3, proved to be poor HBr scavengers. The hindered organic base 4-methyl-2,6-di-*tert*-butylpyridine destroyed the acid bromide, stalling the reaction.

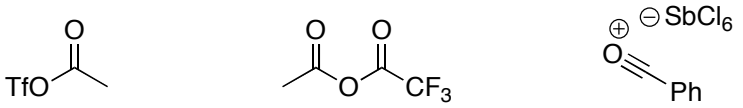
Scavenging HBr with double bonds was also considered. Cyclohexene was tried first and determined to be inefficient as a scavenger. Limonene had been used as an HCl scavenger by others with good results,[91] so it was examined in this reaction. When the dienone was reacted with benzoyl bromide and limonene, no demethylation was observed. However, the yield of **2.4.31** remained around 20% (Equation 2.4.20). Although the starting material had been completely consumed, a large amount of material was lost to decomposition through an unknown pathway.



Equation 2.4.20 Scavenging HBr with limonene

A number of conditions were changed in an effort to improve the reaction. Changing the acid bromide to *p*-nitrobenzoyl bromide or *p*-methoxybenzoyl bromide failed to improve the yield. The addition of Lewis acids ($AlCl_3$, $AlBr_3$) along with the acid bromides did not increase the yield either. Solvent changes from 1,2-dichloroethane ($PhNO_2$, PhCl, toluene, cyclohexane) also provided no better results. An increase in temperature to 120-140 °C in chlorobenzene or nitrobenzene was also met with limited success.

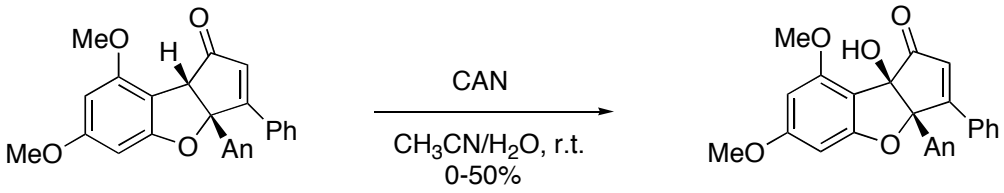
Other noteworthy conditions that failed to produce the product are the use of acyl triflate **2.4.47**, mixed anhydride **2.4.48**, and full acylium ion **2.4.49** (Figure 2.4.4). Iminium catalysis was also investigated to induce the cyclization. It was presumed that the carboxylate present on proline might stabilize the allylic cation upon cyclization. However, proline gave no reaction up to 150 °C, which is not surprising since nitrogen stabilizes the pentadienyl cation to a greater extent than oxygen.[92]



2.4.47 **2.4.48** **2.4.49**

Figure 2.4.4 Other reagents screened for cyclization

While optimization of the cyclization continued, the cyclized material that had been collected was advanced toward rocaglamide. The oxidation of the benzylic position with ceric ammonium nitrate was a bit problematic on this substrate. The yields of **2.4.50** varied significantly from 0-50% (Equation 2.4.21). The product seemed to be getting over-oxidized during work-up of the reaction.

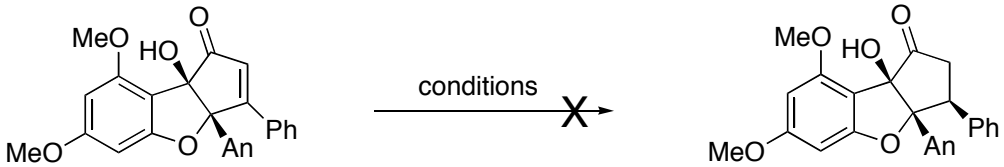


2.4.31 **2.4.50**

Equation 2.4.21 Oxidation of the benzylic position

Although the yield of the oxidation was poor and not reproducible at this time, it was believed that it could be optimized later if the compound was useful. It was critical to know if the reduction of the enone to the *cis* diaryl configuration could be achieved on this substrate. Trost had published the reduction on a similar substrate in his synthesis of rocaglamide.

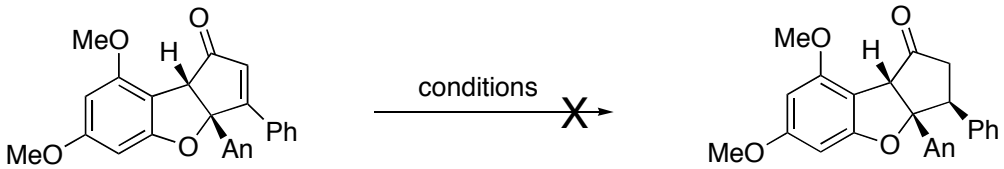
Unfortunately, reactions using catalytic hydrogenation (Pd/C, $Pd/BaSO_4$, PtO_2, $Pd(OH)_2$) were messy, and the crude reaction mixtures did not contain any of the desired cyclopentanone. Copper hydride sources only gave recovered starting material and $Et_3SiH/BF_3{\bullet}OEt_2$ caused the reduction of the benzylic hydroxyl. Taylor had synthesized **2.4.50** during the course of his work on rocaglamide and he too was unable to reduce the enone to cyclopentanone **2.4.44.**



2.4.50 **2.4.44**

Equation 2.4.22 Reduction of enone **2.4.50**

Reduction of cyclopentenone **2.4.31** was also unsuccessful under a number of conditions screened (Equation 2.4.23).



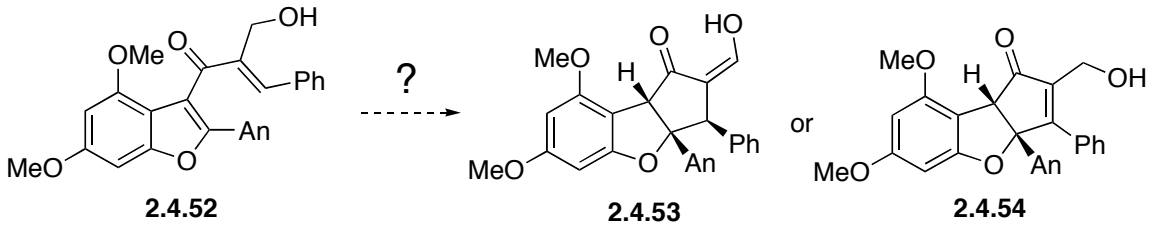
2.4.31 **2.4.51**

Equation 2.4.23 Reduction of enone **2.4.31**

A revision of the strategy was again necessary to overcome the problems associated with this route, since the Nazarov cyclization of the α-protio dienone and subsequent transformations did not provide satisfactory results.

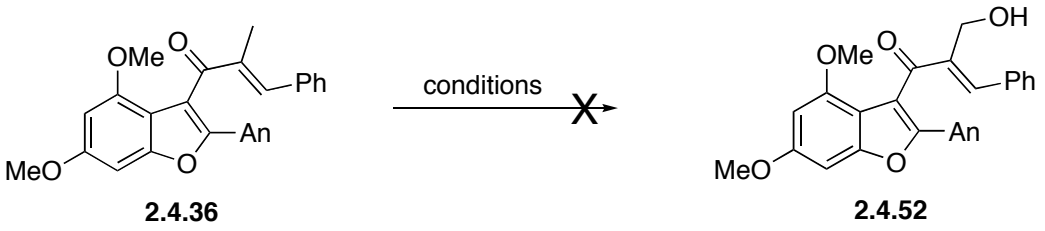
2.4.6 α-Methoxymethyl Dienone

It was obvious that the cyclization was more efficient with substitution at the alpha position of the dienone, for it lowered the activation energy of the cyclization and provided more stable intermediates. The inability to oxidize the methyl substituent after the cyclization occurred in the α-methyl series, however, put an end to that route. Therefore, it was decided that the methyl would be oxidized prior to the cyclization. This should keep the reactivity of the dienone high, while possibly allowing for the double bond to end up exocyclic (Scheme 2.4.16). If it did end up exocyclic, it was possible that the required *cis* configuration of the phenyl and anisyl substituents would predominate.



Scheme 2.4.16 Cyclization of the oxidized α-substituent

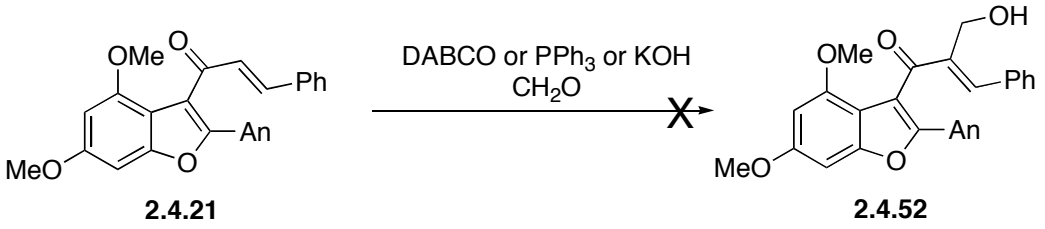
An allylic oxidation of **2.4.36** was first attempted to synthesize **2.4.52** (Equation 2.4.24). Unfortunately, all conditions screened, including SeO_2, $^1O_2$, and DDQ, failed to produce any of the desired product.



2.4.36 **2.4.52**

Equation 2.4.24 Allylic oxidation of dienone

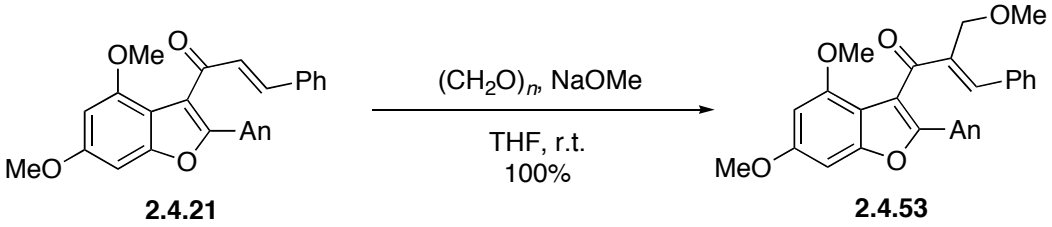
Baylis-Hillman chemistry was next explored to install the extra carbon. Treatment of dienone **2.4.21** with distilled gaseous formaldehyde and DABCO or PPh_3 only returned unreacted starting material (Equation 2.4.25). It was thought that KOH might be a better promoter of the reaction but these conditions did not produce any product either. The use of Et_2AlI to promote the Baylis-Hillman reaction[93] caused a retro Friedel-Crafts reaction of the dienone.



2.4.21 **2.4.52**

Equation 2.4.25 Baylis-Hillman attempt

Methoxide had previously been shown to work well in Baylis-Hillman reactions giving good yields of allylic alcohols.[94] So NaOMe was screened in this reaction. It was believed that methoxide might be more reactive than amines or phosphines in the 1,4-addition, which might increase the concentration of the enolate in solution, thus allowing more efficient trapping by formaldehyde. When dienone **2.4.21** was treated with sodium methoxide and paraformaldehyde in THF, a quantitative yield of allylic methoxyl compound **2.4.53** was obtained (Equation 2.4.26). This product came about by dehydration after trapping of the enolate by formaldehyde, followed by re-addition of methoxide to the double bond terminus. Loss of one methoxide to give the more substituted double bond lead to compound **2.4.53**.

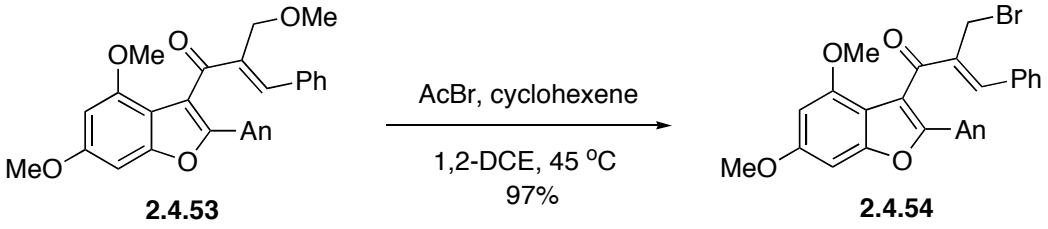


2.4.21 **2.4.53**

Equation 2.4.26 Baylis-Hillman reaction with methoxide

With the α-methoxymethyl dienone in hand, exploration into the Nazarov cyclization of this substrate was begun. Treatment with Lewis acids again caused a retro Friedel-Crafts reaction, so attention turned to the previously discovered acid bromide promoted cyclization conditions. Complete consumption of the starting material was observed when dienone **2.4.53** was treated with AcBr and cyclohexene in 1,2-DCE at 45

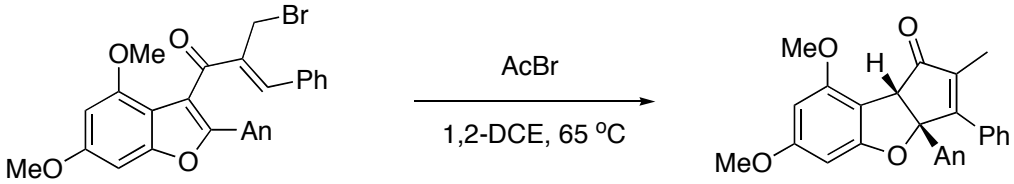
°C. However, the product obtained was allylic bromide **2.4.54** in 97% yield (Equation 2.4.27). It was presumed that cyclohexene was not a good enough scavenger of HBr, and this was causing the loss of the methoxyl.



2.4.53 **2.4.54**

Equation 2.4.27 Formation of allylic bromide

The bromomethyl dienone **2.4.54** was treated with AcBr at 65 °C to determine the products of cyclization. It was observed that cyclization did occur, but the bromide was lost during the transformation. The only product formed in the reaction was cyclopentenone **2.4.38** (Equation 2.4.28).



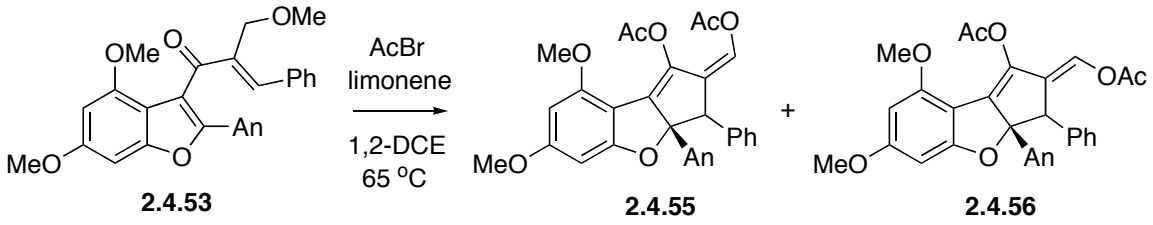
2.4.54 **2.4.38**

Equation 2.4.28 Cyclization of α-bromomethyl dienone

The isolation of the internal alkene from cyclization of the α-bromomethyl dienone **2.4.54** showed that the exo-methylene could indeed isomerize to the more

substituted internal alkene under the reaction conditions. It was unfortunate that the bromide was lost during the cyclization event since oxidation of the methyl substituent had proven to be extremely difficult.

After determining that the α-bromomethyl dienone was of no use, the cyclization of the α-methoxymethyl compound using a more efficient HBr scavenger was examined. Upon treatment of dienone **2.4.53** with AcBr and limonene at 65 ºC, the formation of a single compound by TLC was observed. However, the NMR spectrum showed a mixture of two compounds. Based on the IR data, mass, and NMR spectrum, the two compounds were assigned as a mixture of the dienol acetates **2.4.55** and **2.4.56** (Equation 2.4.29). The mixture of compounds was very unstable and they rapidly degraded when left overnight on the bench. The mixture was not stable to column chromatography either. Therefore, it was necessary use the crude material immediately after it was formed to avoid any degradation.

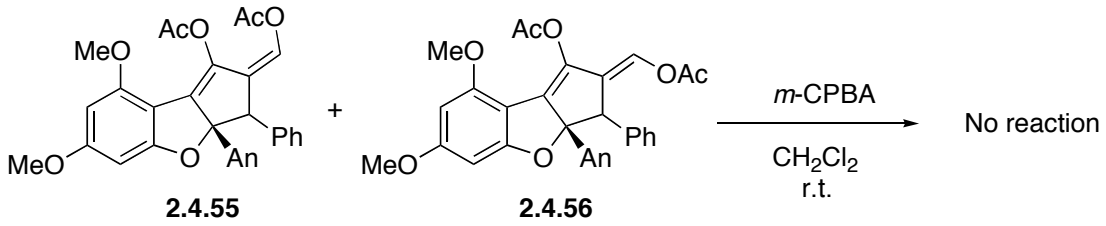


2.4.53 **2.4.55** **2.4.56**

Equation 2.4.29 Nazarov cyclization of α-methoxymethyl dienone

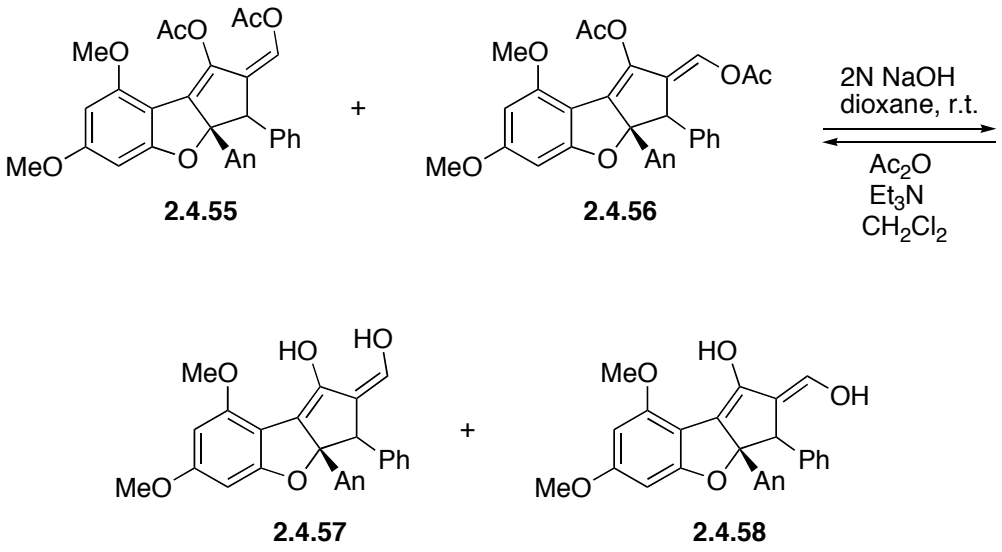
The stereochemistry at the C-3 carbon with the phenyl substituent was unclear and a stable compound that could be more easily identified was desired. To achieve this,

epoxidation of the mixture was attempted. Epoxidation and opening could introduce the tertiary alcohol present in rocaglamide. Treatment of the mixture of acetates with up to 4 equivalents of *m*-CPBA only gave recovered starting material (Equation 2.4.30).



Equation 2.4.30 Unsuccessful epoxidation

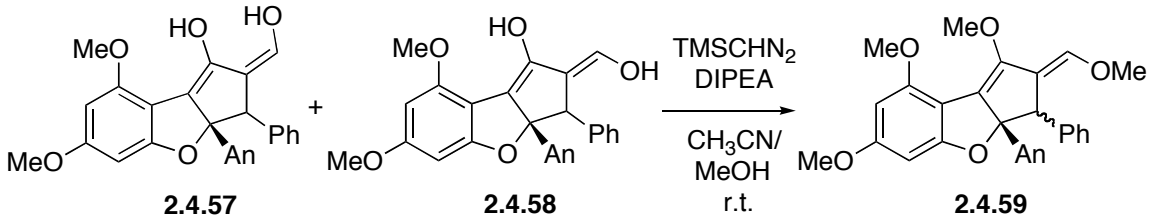
Next, it was thought that cleavage of the acetates might deliver a single stable compound that might be easier to identify. Treatment with K_2CO_3 in methanol at room temperature gave a complex mixture of products. When **2.4.55** and **2.4.56** were treated with 2N NaOH in dioxane at room temperature, a clean reaction ensued that again gave a mixture of two compounds. The structures of the two compounds were once more unclear. They were somewhat stable to column chromatography, but inseparable. The structures were originally assigned as **2.4.57** and **2.4.58** based on the collected data (Scheme 2.4.17). The treatment of **2.4.57** and **2.4.58** with acetic anhydride and triethylamine gave back the mixture of **2.4.55** and **2.4.56**, so it was assumed that the structures were assigned correctly.



Scheme 2.4.17 Cleavage of the acetates

Since the enols **2.4.57** and **2.4.58** were more stable than the acetates, their conversion into a single crystalline compound was attempted. The determination of the stereochemistry at the phenyl substituent was still of interest, as the *cis* orientation of the aromatics was desired.

A number of transformations were tried (oxidations, reductions, functional group transformations) to reach a stable, crystalline compound. All conditions screened always gave mixtures of at least two compounds. When **2.4.55** and **2.4.56** were eventually treated with trimethylsilyldiazomethane, a single compound was obtained (Equation 2.4.31). The structure of the compound had been assigned as **2.4.59** because the small 2.2 Hz *meta* coupling of the aromatic protons on the A-ring in the NMR spectrum seemed consistent with this structure.



Equation 2.4.31 Treatment with $TMSCHN_2$

2.4.59 was crystallized and its structure determined by X-ray crystallography (See Appendix 5). The X-ray crystal structure showed that the originally assigned structure of **2.4.59** was incorrect. The furan ring had been opened at some point during the 3-step transformation, and the actual structure is shown below (Figure 2.4.4). The *meta* coupling observed in the NMR spectrum came from atropisomers. The barrier to rotation about the C2-C6 bond must be slow enough that the two protons appear distinct by NMR spectroscopy.

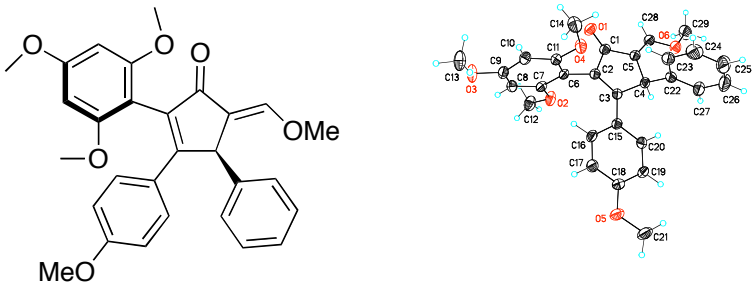
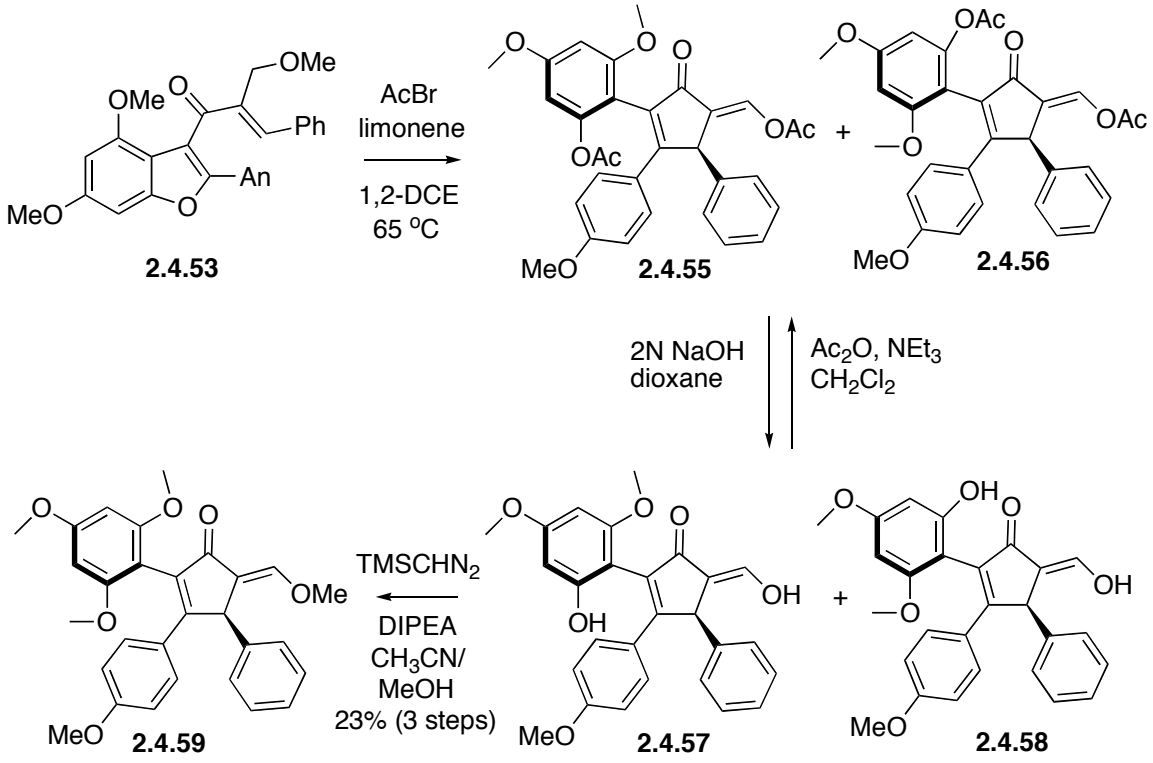


Figure 2.4.4 X-ray structure showing opened furan

After reexamining the data, it now made sense why at least two compounds had appeared in every transformation since the atropisomers were causing this effect.

Therefore, the structures were reassigned based on this new evidence. It was determined that the opening of the furan ring had occurred during the initial cyclization step with AcBr, and the sequence of reactions occurred as shown in Scheme 2.4.18.

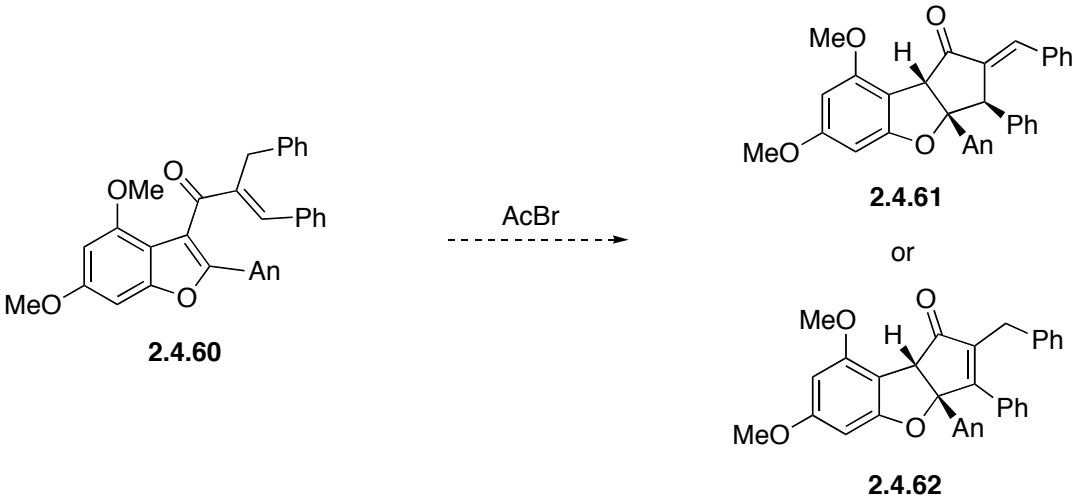


Scheme 2.4.18 Reactions and reassigned structures

With a grasp on the structures of the molecules, the closure benzofuran ring was examined. Unfortunately, under acidic or basic conditions, **2.4.57** and **2.4.58** did not re-close.

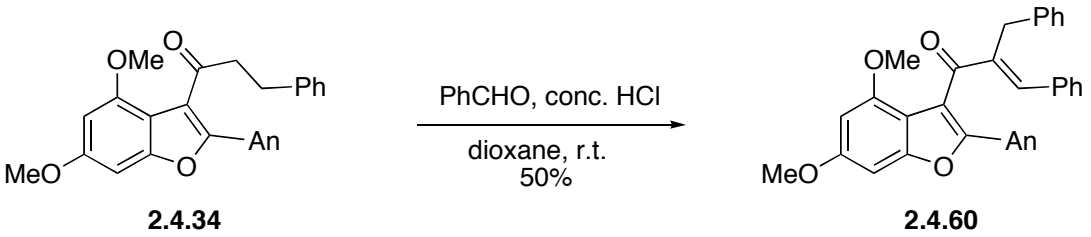
2.4.7 α-Benzyl Dienone

While working with the α-methoxymethyl dienone, experiments were also ongoing with a benzyl group at the alpha position of the dienone. Again the question was raised as to whether the double bond would end up exo- or endocyclic (Equation 2.4.32).



Equation 2.4.32 Proposed cyclization products of α-benzyl dienone

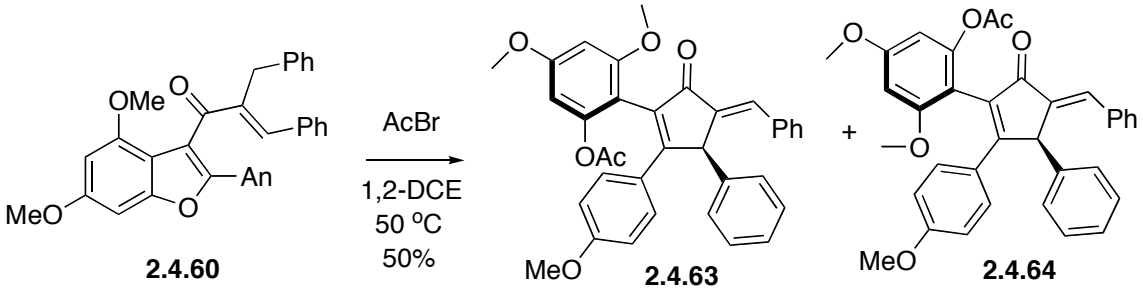
The synthesis of dienone **2.4.60** was straightforward starting from previously synthesized ketone **2.4.34** *via* aldol condensation. Treatment of the ketone with benzaldehyde and concentrated HCl in dioxane gave dienone **2.4.60** in 50% yield (Equation 2.4.33).



2.4.34 **2.4.60**

Equation 2.4.33 Synthesis of α-benzyl dienone

When treated with acetyl bromide in 1,2-DCE, the starting material was consumed and a mixture of two products was obtained (Equation 2.4.34). Unfortunately, the products were again a mixture of atropisomers **2.4.63** and **2.4.64**, which came about *via* cyclization and furan ring opening.



2.4.60 **2.4.63** **2.4.64**

Equation 2.4.34 Cyclization and opening of furan

The inability to prevent the benzofuran ring from opening when the double bond remained exocyclic was troubling and no conditions were found to overcome this problem. Hence, this route using the α-benzyl dienone was discontinued as well.

2.5 Conclusion

A number of routes to rocaglamide have been studied. Successful construction of the tricyclic core was achieved using a novel acid bromide promoted cyclization of a dienone. Unfortunately, conditions were never found to advance the late-stage intermediates to the natural product. Oxidation of the methyl substituent proved to be more difficult than had been anticipated, and the lack of a substituent at the alpha position of the dienone failed to generate good yields in the cyclization.

The propensity of the benzofuran to open when the double bond remained exocyclic was disappointing, as the stereochemistry achieved through the cyclization could not be determined, nor could the benzofuran ring be reinstalled.

Efforts are ongoing to determine an appropriate substituent to install at the α-position of the dienone to affect the cyclization in good yield, without causing the opening of the benzofuran ring system. The introduction of a bromide at the α-position should provide the extra stabilization of the allylic cation required to promote the cyclization effectively. Cyclization of an α-bromo dienone would also lead to the internal double bond after proton loss, which should prevent the furan from opening, as well as give a handle to introduce the amide functionality *via* palladium-catalyzed carbonylation of the vinyl bromide.

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3. Experimental Conditions and Compound Data

3.1 General Information

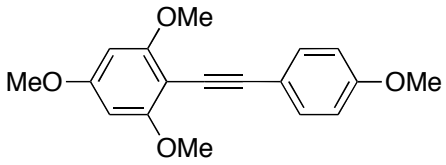
Melting points were measured on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet FT-IR spectrophotometer as thin films on a NaCl disc. ^{1}H NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz as solutions in the indicated solvents and are reported in parts per million (ppm) relative to tetramethylsilane and referenced internally to protonated residual solvent. ^{13}C spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer, and are referenced internally to the indicated solvent. Mass spectra were obtained on either a VG ZAB2E or a Finnegan TSQ70 spectrometer using CI.

All reactions requiring anhydrous conditions were performed in oven-dried (110° C for >30 min.) or flame-dried glassware under an atmosphere of argon. Anhydrous solvents were distilled under dry nitrogen as follows: CH_2Cl_2 and 1,2-DCE from CaH_2; THF and Et_2O from sodium benzophenone ketyl. Reagents were purified according to methods in Armarego and Chai.[1] Alkyllithium reagents were titrated against N-benzylamide in accordance with the literature procedure.[2] Reactions were monitored using thin-layer chromatography on glass-backed plates coated with silica gel containing a fluorescent indicator (25 μm Silica Gel 60, F_{254}) and were visualized using standard techniques: UV fluorescence (254 or 365 nm); phosphomolybdic acid stain. Flash

column chromatography was preformed on silica gel (Kieselgel 60, 40-60 μm), with the indicated eluant, according to the method of Still et. al.[3]

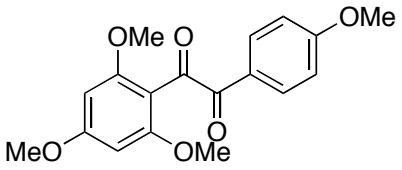
3.2 Experimental Conditions and Compound Data

1,3,5-Trimethoxy-2-(4-methoxyphenylethynyl)benzene (1.5.21)



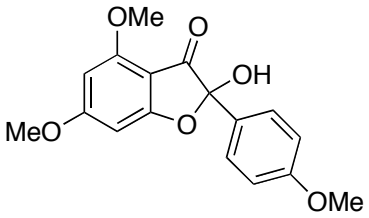
To a mixture of 2-iodo-1,3,5-trimethoxybenzene (8.75 g, 29.8 mmol) and 4-methoxyphenylacetylene (7.88 g, 59.6 mmol) in dry DMF (60 mL) was added triethylamine (60 mL) followed by CuI (0.167 g, 0.877 mmol) and $Pd(PPh_3)_2Cl_2$ (0.635 g, 0.905 mmol). The solution was heated to 80 ºC for 16 hours, then concentrated *via* rotary evaporation. The dark brown oil was partitioned between CH_2Cl_2 (250 mL) and water (250 mL). The separated organic layer was washed with water (200 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (SiO_2, 20% EtOAc in hexane) gave the title compound as a yellow-orange solid (8.69 g, 98%). Mp. 120-121 ºC. R_f = 0.25 (25% EtOAc in hexane). IR (thin film) 2939, 2838, 1608, 1576 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.7 Hz), 6.85 (2H, d, *J* = 8.7 Hz), 6.13 (2H, s), 3.89 (6H, s), 3.83 (3H, s), 3.82 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 161.2, 158.9, 132.7, 116.2, 113.5, 95.9, 94.4, 90.3, 80.3, 55.8, 55.1, 55.0. HRMS calculated for $C_{18}H_{19}O_4$ (MH+) 299.1283. Found 299.1279.

1-(2,4,6-trimethoxyphenyl)-2-(4-methoxyphenyl)ethane-1,2-dione (1.5.3)



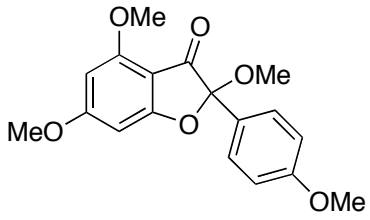
To a stirred solution of acetylene **1.5.21** (2.34 g, 7.84 mmol) in acetonitrile (20 mL), water (30 mL) and carbon tetrachloride (20 mL) was added $NaIO_4$ (6.88 g, 32.2 mmol) followed by $RuCl_3$ (35.8 mg, 0.172mmol). The solution was stirred vigorously for 1 hour, then diluted with water (70 mL) and extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered through Celite and concentrated. Purification by flash column chromatography (SiO_2, 50% EtOAc in hexane) yielded the title compound as a pale yellow solid (1.31 g, 51%). Mp. 134-136 ºC. R_f = 0.21 (50% EtOAc in hexane). IR (thin film) 1666, 1601, 1576 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.6 Hz), 6.91 (2H, d, *J* = 8.6 Hz), 6.06 (2H, s), 3.83 (3H, s), 3.80 (3H, s), 3.64 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 190.9, 165.8, 163.4, 162.9, 131.7, 125.9, 113.5, 107.6, 90.8, 55.6, 55.4, 55.3. HRMS calculated for $C_{18}H_{19}O_6$ (MH+) 331.1182. Found 331.1190.

2-hydroxy-4,6-dimethoxy2-(4-methoxyphenyl)benzofuran-3(2*H*)-one (1.5.31)



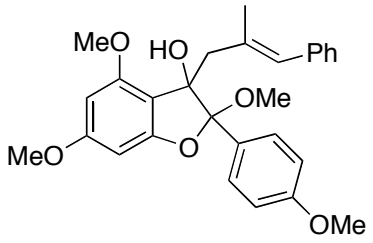
BCl_3 (1.0 M solution in CH_2Cl_2, 11.8 mL, 11.8 mmol) was added to a stirred solution of diketone **1.5.3** in anhydrous CH_2Cl_2 (25 mL) at room temperature. The solution was stirred at room temperature for 1 hour and quenched with the addition of 2N HCl (12 mL). The biphasic mixture was stirred for 30 minutes. The organic layer was then separated, dried (Na_2SO_4), filtered and concentrated *via* rotary evaporation. Purification by column chromatography (SiO_2, 35% EtOAc in hexane) yielded the title compound as a pale yellow solid (1.01 g, 82 %). Mp. 124-126 ºC. R_f = 0.32 (50% EtOAc in hexane). IR (thin film) 3420, 2940,1674, 1629, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.8 Hz), 6.93 (2H, d, *J* = 8.8 Hz), 6.10 (1H, d, *J* = 1.8 Hz), 5.83 (1H, d, *J* = 1.8 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.45 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 168.5, 167.4, 163.9, 162.4, 131.2, 131.1, 125.8, 113.9, 103.5, 93.7, 91.0, 55.7, 55.4, 55.3. HRMS calculated for $C_{17}H_{17}O_6$ (MH+) 317.1025. Found 317.1029.

2,4,6-trimethoxy-2-(4-methoxyphenyl)benzofuran-3(2*H*)-one (1.5.4)



Concentrated sulfuric acid (5 drops) was added to a stirred solution of hydroxyketone **1.5.31** (1.05 g, 3.38 mmol) and trimethylorthoformate (10.5 mL, 96.0 mmol) in methanol (30 mL). The solution was heated at reflux for 16 hours, then cooled to room temperature and diluted with Et_2O (100 mL). The solution was washed with 5% aqueous NaOH (50 mL) and brine (50 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2, 30% EtOAc in hexane) yielded the title compound as a yellow foam (1.10 g, 100%). R_f = 0.35 (50% EtOAc in hexane). IR (thin film) 2940, 2838, 1708, 1619, 1592 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (2H, dd, *J* = 2.0, 6.8 Hz), 6.82 (2H, dd, *J* = 2.0, 6.8 Hz), 6.23 (1H, d, *J* = 1.9 Hz), 5.98 (1H, d, *J* = 1.7 Hz), 3.84 (3H, s), 3.82 (3H, s), 3.72 (3H, s), 3.38 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 173.3, 170.5, 160.2, 159.5, 127.4, 126.9, 113.6, 107.8, 102.9, 93.0, 88.7, 55.9, 55.8, 55.0, 52.2. HRMS calculated for $C_{18}H_{19}O_6$ (MH+) 331.1182. Found 331.1185.

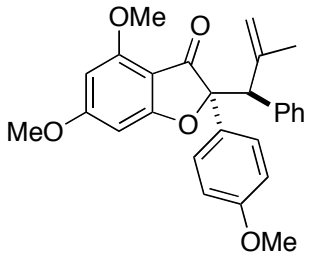
2,3-dihyro-2,4,6-trimethoxy-2-(4-methoxyphenyl)-3-((E)-2-methyl-3-phenylallyl)benzofuran-3-ol (2.1.1)



n-Butyllithium (2.49 M solution in hexane, 1.35 mL, 3.36 mmol) was added to a solution of (2-methylprop-1-enyl)benzene (0.211 g, 1.60 mmol) and TMEDA (0.48 mL, 3.20 mmol) in anhydrous diethyl ether (5.0 mL) at –78°C. The solution was warmed to 22°C and stirred for 22 hours. To this red-colored solution was added ketone **1.5.4** (0.105 g, 0.318 mmol) in Et_2O (0.50 mL) and stirring was continued for a further 14 hrs. The reaction was quenched with the addition of water (15 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The crude product was purified by flash column chromatography (SiO_2, 10–25% EtOAc in hexane) to give the title compound as a colorless oil (32 mg, 22%). R_f = 0.22 (25% EtOAc in hexane). IR (thin film) 3504, 2939, 2837, 1626, 1611, 1598 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.59 (2H, dd, *J* = 2.0, 6.7 Hz), 7.38 (2H, d, *J* = 7.4 Hz), 7.20–7.12 (2H, m), 7.02 (1H, t, *J* = 7.3 Hz), 6.82 (2H, dd, *J* = 2.0, 6.8 Hz), 6.50 (1H, s), 6.24 (1H, d, *J* = 2.1 Hz), 6.02 (1H, d, *J* = 2.1 Hz), 3.80 (1H, d, *J* = 14.4 Hz), 3.72 (1H, d, *J* = 14.6 Hz), 3.32 (3H, s), 3.29 (3H, s), 3.17 (3H, s), 3.11 (3H, s), 2.07 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.0, 159.2,159.0, 157.5, 138.9, 138.3, 129.9, 128.5, 127.9, 126.7, 126.7, 125.4, 115.9, 113.0, 112.4, 92.2, 89.4,

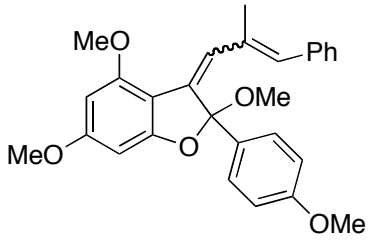
83.3, 55.5, 55.3, 55.0, 50.2, 35.5, 25.9. HRMS calculated for $C_{28}H_{31}O_6$ (MH+) 463.2121. Found 463.2118.

***trans*-Benzofuranone (2.1.6)**



To crude alcohol **2.1.5** (estimated 1.24 mmol) in $CHCl_3$ (2 mL) was added a few drops BCl_3. The dark green solution was stirred at room temperature for 45 minutes. Water (5 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2, 20% EtOAc in hexane) yielded the title compound as colorless solid (58.9 mg, 11% over 2 steps). R_f = 0.18 (30% EtOAc in hexane). IR (thin film) 2965, 2840, 1703, 1619, 1594, 1510 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 7.36 (2H, d, *J* = 8.8 Hz), 7.30–7.26 (2H, m), 7.15-7.12 (3H, m), 6.6 (2H, d, *J* = 8.8 Hz), 6.37 (1H, s), 6.01 (1H, s), 5.05 (1H, s), 4.78 (1H, s), 4.38 (1H, s), 3.91 (3H, s), 3.85 (3H, s), 3.67 (3H, s), 1.63 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 169.5, 159.2, 158.6, 143.2, 138.1, 129.9, 129.7, 129.3, 127.6, 127.5, 126.1, 125.9, 114.9, 113.3, 113.2, 95.1, 92.9, 88.6, 58.4, 55.8, 55.6, 54.9, 22.9. HRMS calculated for $C_{27}H_{27}O_5$ (MH+) 431.1859. Found 431.1858.

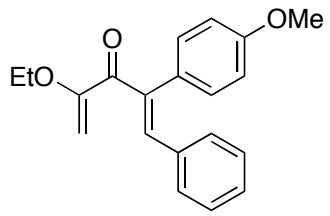
Diene (2.1.2)



p-Toluenesulfonyl chloride (31.0 mg, 0.165 mmol) was added to a stirred solution of alcohol **2.1.1** (32.4 mg, 0.070 mmol) in a mixture of pyridine (0.2 mL) and 1,2-dichloroethane (1 mL). The solution was heated at 50 °C for a period of 4 hours, at which time the yellow solution was allowed to cool to room temperature. The reaction mixture was partitioned between EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated by rotary evaporation to yield the title compound as a pale yellow oil (14.0 mg, 45%) as an approximately 65:35 mixture of geometric isomers. R_f 0.50 (35% EtOAc in hexane). IR (thin film) 3000, 2936, 2836, 1618, 1590 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.94(0.65H, s), 7.53– 7.42 (2.35H, m), 7.39–7.08 (5H, m), 6.86–6.78 (2H, m), 6.58 (0.35H, br s), 6.28 (0.65H, br s), 6.10 (0.35H, d, J = 2.1 Hz), 6.08 (0.35H, d, J = 2.0 Hz), 6.03 (1.3H, s), 3.95 (1.05H, s), 3.79 (1.05H, s), 3.78 (1.05H, s), 3.77 (1.95H, s), 3.76 (1.95H, s), 3.73 (1.95H, s), 3.44 (1.05H, s), 3.38 (1.95H, s), 1.71 (1.95H, d, J = 1.0), 1.61 (1.05H, s). ^{13}C NMR (75 MHz, $CDCl_3$, several signals are not distinguishable) δ 162.4, 161.0, 160.8, 159.5, 159.3, 156.5, 138.0, 137.9, 134.6, 133.6, 133.4, 133.0, 131.6, 131.1, 129.9, 129.3, 128.9, 127.7, 127.6, 127.2, 126.9, 126.0, 124.2, 113.1, 112.9, 91.6, 91.5, 87.4, 55.3, 55.2, 55.1, 55.0, 54.9, 50.6, 50.6, 23.5, 17.3. HRMS calculated for $C_{28}H_{29}O_5$

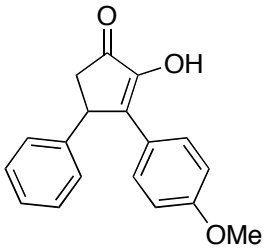
(MH+) 445.2015. Found 445.2013.

(E)-4-ethoxy-2-(4-methoxyphenyl)-1-phenylpenta-1,4-diene-3-one (2.2.9)



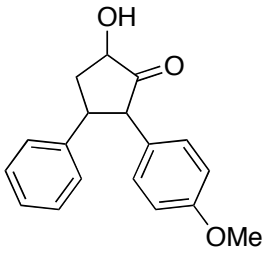
To ethyl vinyl ether (3.41 mL, 35.4 mmol) and TMEDA (5.31 mL, 35.4 mmol) in dry Et_2O (40 mL) at 0 ºC under argon was added *n*-BuLi (2.48 M, 14.3 mL, 35.43 mmol). The reaction mixture was warmed to room temperature over 45 minutes, then cooled again to 0 ºC. (E)-2-(4-methoxyphenyl)-3-phenylacrylic acid[4] (3.00 g, 11.8 mmol) in dry THF (40 mL) was added and the mixture was stirred for 20 minutes at 0 ºC. The mixture was then poured onto brine (50 mL) and extracted with Et_2O (2 X 50 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *via* rotary evaporation. The product was obtained as an orange oil (3.50 g, 96 %). R_f = 0.50 (30% EtOAc in hexane). IR (thin film) 2933, 2837, 1663, 1606, 1512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (1H, s), 7.20-7.16 (4H, m), 7.12 (2H, d, *J* = 8.1 Hz), 6.85 (2H, d, *J* = 8.1 Hz), 5.01 (1H, d, *J* = 2.2 Hz), 4.59 (1H, d, *J* = 2.9 Hz), 3.82 (3H, s), 3.73 (2H, q, *J* = 7.36 Hz), 1.26 (3H, t, *J* = 7.36 Hz). ^{13}C NMR (75 MHz, DMSO-D_6) δ 193.2, 159.3, 158.1, 139.7, 139.0, 134.9, 130.9, 130.5, 129.7, 129.6, 128.9, 128.4, 114.6, 57.2, 55.5, 14.4. HRMS calculated for $C_{20}H_{21}O_3$ (MH+) 309.1491. Found 309.1491.

2-hydroxy-3-(4-methoxyphenyl)-4-phenylcyclopent-2-enone (2.2.8)



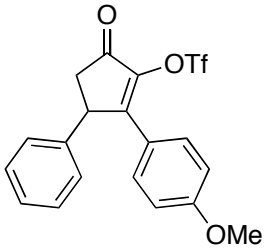
To dienone **2.2.9** (733 mg, 2.38 mmol) in MeOH (10 mL) at room temperature was added concentrated H_2SO_4 (0.2 mL). The mixture was stirred at room temperature for 1.5 hours, then poured onto water (20 mL). The reaction mixture was extracted with EtOAc (2 X 25 mL) and organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *via* rotary evaporation. Purification by flash column chromatography (SiO_2, 20-25% EtOAc in hexane) yielded the title compound as an off-white solid (633 mg, 95%). Mp. 167-169 °C. R_f = 0.32 (30% EtOAc in hexane). IR (thin film) 3275, 2959, 2837, 1683, 1603, 1514 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 9.6 Hz), 7.18-7.05 (5H, m), 6.73 (2H, d, *J* = 9.6 Hz), 4.34 (1H, dd, *J* = 1.5, 6.6 Hz), 3.67 (3H, s), 2.97 (1H, dd, *J* = 6.6, 19 Hz), 2.25 (1H, dd, *J* = 1.5, 19 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 160.1, 148.5, 131.0, 130.7, 129.0, 128.2, 126.9, 126.8, 114.1, 113.8, 55.1, 42.6, 41.6. HRMS calculated for $C_{18}H_{16}O_3$ (MH+) 280.1092. Found 280.1099.

5-hydroxy-2-(4-methoxyphenyl)-3-phenylcyclopentaone (2.2.14)



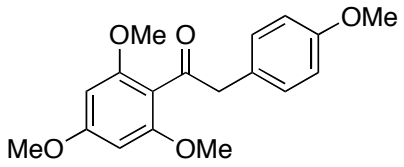
To ketone **2.2.8** (145 mg, 0.56 mmol) in dry THF (3 mL) at -78 ºC was added LAH (2M in THF, 0.65 mL, 1.29 mmol). The reaction mixture was stirred at -78 ºC for 15 min, then EtOAc (10 mL) was added and the mixture was warmed to room temperature over 30 minutes. Saturated aq. Na_2SO_4 (10 mL) was added and the mixture was stirred vigorously for 30 minutes. Solid Na_2SO_4 was added until it remained granular. The solid was filtered and washed with EtOAc. The organic layer was concentrated by rotary evaporation. Purification by flash column chromatography (SiO_2, 30% EtOAc in hexane) yielded the title compound as an orange foam (134 mg, 85%). R_f = 0.16 (30% EtOAc in hexane). IR (thin film) 3423, 2956, 2930, 2836, 1749, 1514 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.19-7.13 (3H, m), 7.07-7.05 (2H, m), 6.85 (2H, dd, *J* = 2.2, 8.8 Hz), 6.70 (2H, dd, *J* = 2.2, 8.8 Hz), 4.30 (1H, dd, *J* = 8.1, 11.7 Hz), 3.65 (3H, s), 3.34-3.25 (1H, m), 2.76-2.67 (1H, m), 1.95 (1H, q, *J* = 11.7 Hz), 1.21-1.13 (1H, m). HRMS calculated for $C_{18}H_{19}O_3$ (MH+) 282.1332. Found 282.1334.

2-(4-methoxyphenyl)-5-oxo-3-phenylcyclopent-1-enyl-trifluoromethanesulfonate (2.2.16)



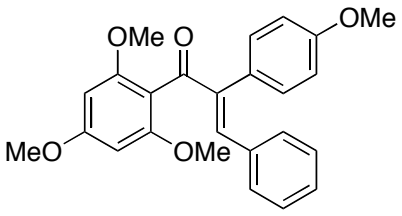
To enol **2.2.8** (254 mg, 0.91 mmol) in dry CH_2Cl_2 (4 mL) at -78 ºC under argon was added triethylamine (0.25 mL, 1.80 mmol) and triflic anhydride (0.20 mL, 1.18 mmol). The reaction mixture was warmed to room temperature over 30 minutes, then water (10 mL) was added. The solution was diluted with CH_2Cl_2 (15 mL) and the phases were separated. The organic layer was concentrated by rotary evaporation. Purification by flash column chromatography (SiO_2, 20% EtOAc in hexane) yielded the title compound as a tan solid (332 mg, 89%). Mp. 121-123 ºC. R_f = 0.43 (30% EtOAc in hexane). IR (thin film) 2934, 2840, 1723, 1603, 1513, 1423 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (2H, dd, *J* = 2.2, 6.6 Hz), 7.31-7.22 (3H, m), 7.21-7.14 (2H, m), 6.85 (2H, dd, *J* = 2.2, 6.6 Hz), 4.57 (1H, dd, *J* = 2.2, 7.36 Hz), 3.80 (3H, s), 3.13 (1H, dd, *J* = 7.36, 19.1 Hz), 2.47 (1H, dd, *J* = 1.5, 19.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 162.2, 159.7, 142.3, 141.3, 131.0, 129.4, 127.5, 126.9, 122.2, 114.4, 113.9, 55.3, 43.2, 42.5. HRMS calculated for $C_{19}H_{16}O_5SF_3$ (MH+) 413.0671. Found 413.6071.

1-(2,4,6-trimethoxyphenyl)-2-(4-methoxyphenyl)ethanone (2.2.20)



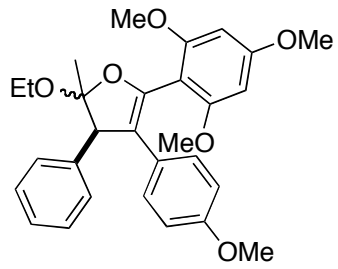
To 4-methoxyphenylacetic acid (3.50 g, 21.0 mmol) in dry benzene (6 mL) at 0 ºC under argon was added oxalyl chloride (3 mL). The reaction mixture was allowed to warm to room temperature over 16 hours. The solvent was removed by rotary evaporation and the residue was dissolved in dry CH_2Cl_2 (25 mL). 1,3,5-trimethoxybenzene (3.46 g, 20.6 mmol) was added and the solution was cooled to 0 ºC. $AlCl_3$ (3.08 g, 23.1 mmol) was slowly added to the reaction mixture over 10 minutes and the reaction was stirred at 0 ºC for one hour, then allowed to warm to room temperature over 14 hours. The reaction mixture was poured onto ice/water (50 mL) and diluted with CH_2Cl_2 (50 mL). The phases were separated and the organic layer was washed with saturated $NaHCO_3$ (10 mL), then dried (Na_2SO_4), filtered and concentrated to give the title compound as a yellow oil which was used without further purification (6.5 g, 100 %). R_f = 0.22 (30% EtOAc in hexane). IR (thin film) 2936, 2835, 1697, 1606, 1513 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (2H, d, *J* = 8.1 Hz), 6.70 (2H, d, *J* = 8.8 Hz), 5.95 (2H, s), 3.86 (2H, s), 3.69 (3H, s), 3.66 (3H, s), 3.62 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 162.2, 158.1, 157.9, 130.6, 126.8, 113.4, 90.4, 90.3, 55.6, 55.2, 55.0, 50.4. HRMS calculated for $C_{18}H_{21}O_5$ (MH+) 317.1396. Found 317.1389.

(E)-1-(2,4,6-trimethoxyphenyl)-2-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (2.2.21)



To ketone **2.2.20** (614 mg, 1.94 mmol) and benzaldehyde (0.20 mL, 1.94 mmol) in dry benzene (5 mL) was added piperidine (0.25 mL) and glacial acetic acid (0.5 mL). The solution was heated at reflux with a dean-stark trap for 26 hours. The reaction mixture was cooled to room temperature and poured onto water (15 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. Purification by flash column chromatography (SiO_2, 30% EtOAc in hexane) yielded the title compound as a yellow solid (599 mg, 76%). Mp. 117-118 ºC. R_f = 0.23 (30% EtOAc in hexane). IR (thin film) 2996, 2932, 2839, 1653, 1604, 1511 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.1 Hz), 7.17-7.12 (4H, m), 7.05-7.03 (2H, m), 6.86 (2H, d, *J* = 8.1 Hz), 6.10 (2H, s), 3.79 (3H, s), 3.78 (3H, s), 3.73 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 162.1, 159.0, 158.4, 142.4, 140.8, 140.7, 135.4, 131.0, 130.6, 128.7, 128.4, 128.1, 113.8, 90.6, 55.8, 55.4, 55.1. HRMS calculated for $C_{25}H_{25}O_5$ (MH+) 405.1706. Found 405.1702.

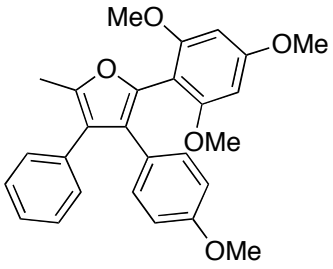
2-ethoxy-2,3-dihydro-5-(2,4,6-trimethoxyphenyl)-4-(4-methoxyphenyl)-2-methyl-3-phenylfuran (2.2.22)



To ethyl vinyl ether (0.03 mL, 0.32 mmol) in dry THF (0.6 mL) at -78 ºC under argon was added *t*-BuLi (1.48 M in pentane, 0.44 mL, 0.64 mmol) dropwise. The mixture was allowed to warm to room temperature over 45 minutes, then cooled to -78 ºC again. Enone **2.2.21** (65.1 mg, 0.16 mmol) in dry THF (0.6 mL) was added and the reaction mixture was stirred at -78 ºC for 5 minutes. Water (3 mL) was added and the reaction mixture was warmed to room temperature over 20 minutes. The mixture was extracted with EtOAc (10 mL) and the organic extract was dried (Na_2SO_4), filtered and concentrated by rotary evaporation. Purification by flash column chromatography (SiO_2, 20% EtOAc in hexane) yielded the title compound as a mixture of diastereomers as a colorless oil (66 mg, 87%). R_f = 0.43 (30% EtOAc in hexane). IR (thin film) 2937, 2837, 1603, 1515 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.18 (5H, m), 6.87 (1H, d, *J* = 8.8 Hz), 6.80 (1H, d, *J* = 8.8 Hz), 6.53 (2H, d, *J* = 8.8 Hz), 6.20 (2H, s), 4.38 (0.5H, s), 4.28 (0.5H, s), 3.87 (1.5H, s), 3.83 (1.5H, s), 3.77 (6H, s), 3.64 (3H, s), 3.52 (2H, q, *J* = 6.6 Hz), 1.76 (1.5H, s), 1.58 (1.5H, s), 0.82 (3H, q, *J* = 6.6Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 162.3, 156.8, 156.7, 143.8, 143.5, 140.3, 138.3, 130.1, 129.1, 128.5, 127.9, 127.4, 127.2, 126.9, 126.2, 115.4, 115.1, 113.6, 113.3, 113.1, 109.0, 108.8, 103.6, 91.2,

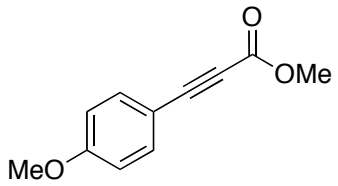
91.0, 61.0, 60.7, 58.2, 57.2, 55.9, 55.4, 54.9, 30.9, 25.2, 21.7, 15.9, 15.3. HRMS calculated for $C_{29}H_{32}O_6$ (MH+) 476.2199. Found 476.2199.

2-(2,4,6-trimethoxyphenyl)-3-(4-methoxyphenyl)-5-methyl-4-phenylfuran (2.2.23)



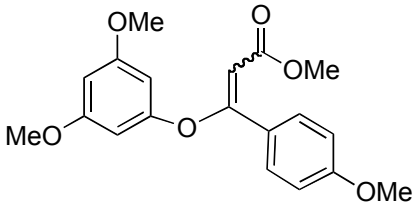
To dihydrofuran **2.2.22** in a 1:1 mixture of dioxane and water was added a few drops of concentrated H_2SO_4. After 5 minutes a tan solid crashed out of the solution. The solid was collected by filtration and washed with water to yield the product as a tan solid. The yield was not determined. Mp. 149-150 ºC. R_f = 0.43 (30% EtOAc in hexane). IR (thin film) 2960, 2936, 2837, 1608, 1584, 1516 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.22-7.16 (5H, m), 6.86 (2H, d, *J* = 8.1 Hz), 6.62 (2H, d, *J* = 8.8 Hz), 6.08 (2H, s), 3.81 (3H, s), 3.70 (3H, s), 3.56 (6H, s), 2.41 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 160.2, 157.7, 148.1, 133.9, 130.0, 127.9, 127.8, 126.9, 126.0, 124.3, 121.5, 120.6, 112.9, 90.9, 90.7, 55.8, 55.3, 55.0, 12.8. HRMS calculated for $C_{27}H_{27}O_5$ (MH+) 431.1857. Found 431.1858.

Methyl-3-(4-methoxyphenyl)propiolate (2.3.4)



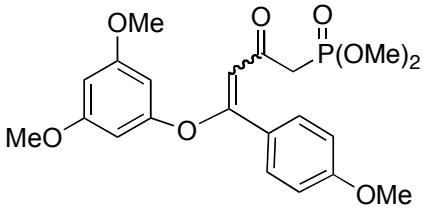
To 4-methoxyphenylacetylene (4.0 g, 30.3 mmol) in anhydrous THF (100 mL) at -78ºC under an atmosphere of argon, was added *n*-BuLi (2.4 M, 15.8 mL, 37.9 mmol). The solution was warmed to room temperature over 30 min. The solution was then re-cooled to -78ºC and methyl chloroformate (2.58 mL, 33.3 mmol) was added. The solution was warmed to room temperature over 1 hour. The reaction was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with water (20 mL), dried (Na_2SO_4), filtered and concentrated *via* rotary evaporation. Purification *via* flash column chromatography (SiO_2 5-20% EtOAc in hexane) afforded ester **2.3.4** as a light yellow solid (4.51 g, 78%). R_f = 0.49 (30% EtOAc in hexanes) Mp. 42-43 ºC IR (thin film) 2951, 2839, 1706, 1603, 1509 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (2H, dd, *J* = 2.0, 6.7 Hz), 6.89 (2H, dd, *J* = 2.0, 6.7 Hz), 3.843 (3H, s), 3.836 (3H, s). ^{13}C NMR(75 MHz, $CDCl_3$) δ 161.5, 154.7, 135.0, 114.3, 111.2, 87.4, 79.8, 55.4, 52.7. HRMS calculated for $C_{11}H_{11}O_3$ (MH+) 191.0708. Found 191.0712.

(E,Z)-Methyl-3-(3,5-dimethoxyphenoxy)-3-(4-methoxyphenyl)acrylate (2.3.3)



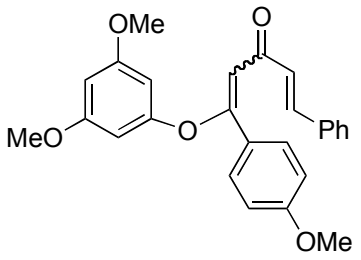
3,5-dimethoxyphenol (926 mg, 6.02 mmol), acetylene **2.3.4** (1.16 g, 6.015 mmol), and DABCO (135 mg, 1.20 mmol) were dissolved in wet DMF (50 mL). The solution was heated at 100° C for 14 hours. The solution was cooled to room temperature and water (50 mL) was added. The aqueous layer was extracted with diethyl ether (2 x 100 mL) and the ethereal solution was washed with water (4 x 50 mL) and saturated aqueous NaCl (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield the crude product as a yellow paste (2.01 g, 97%). R_f = 0.40 (30% EtOAC in hexane) The crude product was taken on as a 5:1 E/Z mixture of diastereomers. IR (thin film) 3007, 2948, 1723, 1606, 1512 cm^{-1}. E-isomer- ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (2H, dd, *J* = 1.6, 8.9 Hz), 6.85 (2H, dd, *J* = 1.9, 8.8 Hz), 6.15 (2H, d, *J* = 2 Hz), 6.09 (1H, d, *J* = 2 Hz), 6.07 (1H, s), 3.81 (3H, s), 3.72 (6H, s), 3.69 (3H, s). ^{13}C NMR(75MHz, $CDCl_3$) δ 165.0, 161.7, 161.6, 161.4, 158.7, 131.1, 128.6, 114.2, 95.1, 94.5, 94.1, 55.5, 55.34, 55.31, 51.3. Z-isomer ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (2H, dd, *J* = 2.0, 8.8 Hz), 6.94 (2H, dd, *J* = 1.9, 8.8 Hz), 6.31 (1H, d, *J* = 2.2 Hz), 6.28 (2H, d, *J* = 2.2 Hz), 5.25 (1H, s), 3.86 (3H, s), 3.78 (6H, s), 3.60 (3H, s). ^{13}C (75MHz, $CDCl_3$) δ 179.0, 161.6, 161.2, 158.8, 155.8, 131.1, 128.6, 114.2, 99.6, 97.4, 95.1, 55.5, 55.3, 51.0. HRMS calculated for $C_{19}H_{20}O_6$ (MH+) 344.1260. Found 344.1260.

(*E,Z*)-dimethyl-4-(3,5-dimethoxyphenoxy)-4-(4-methoxyphenyl)-2-oxobut-3-enylphosphonate (2.3.6)



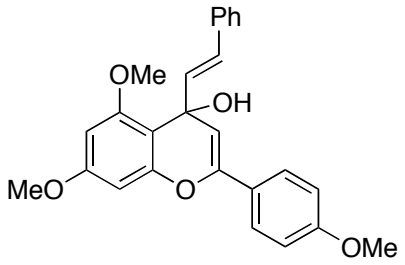
To dimethyl methylphosphonate (0.42 mL, 3.85 mmol) in anhydrous THF (10 mL) at -78 ºC under an atmosphere of argon, was added *n*-BuLi (2.49 M, 1.62 mL, 4.038 mmol). This solution was stirred at -78 ºC for 15 minutes, when ester **2.3.3** (444 mg, 1.28 mmol) in anhydrous THF (8 mL + 2 mL rinse) was added dropwise. The reaction was stirred at -78 ºC for 15 minutes and then quenched with 0.5 N HCl (30 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Compound **2.3.6** was purified by flash column chromatography (SiO_2 eluting with 100% EtOAc) and isolated as a yellow oil (559 mg, 80%). R_f = 0.28 (100% EtOAc). Mixture of diastereomers. IR (thin film) 3006, 2955, 2835, 1681, 1600, 1510, 1475 cm^{-1}. ^1H NMR major component (300 MHz, $CDCl_3$) δ 7.51 (2H, dd, *J* = 1.8, 7.5 Hz), 6.84 (2H, dd, *J* = 2.0, 7.8 Hz), 6.30 (1H, s), 6.14 (2H, d, *J* = 2.0 Hz), 6.11 (1H, d, *J* = 2.0 Hz), 3.81 (3H, s), 3.78 (3H, s), 3.74 (3H, s), 3.72 (6H, s), 3.47 (1H, s), 3.40 (1H, s). ^{13}C NMR (75MHz, $CDCl_3$) δ 189.5 (d, $J_{C,P}$ = 7.3 Hz), 169.8, 161.7, 161.4, 161.37, 129.1, 125.5, 114.2, 99.5, 95.9, 95.0, 55.26, 55.23, 52.8 (d, $J_{C,P}$ = 7.1 Hz), 40.8 (d, $J_{C,P}$ = 121.2 Hz). HRMS calculated for $C_{21}H_{26}O_8P$ (MH+) 437.1365. Found 437.1365.

(1(*E,Z)*,4*E*)-1-(3,5-dimethoxyphenoxy)-1-(4-methoxyphenyl)-5-phenylpenta-1,4-dien-3-one (2.3.2)



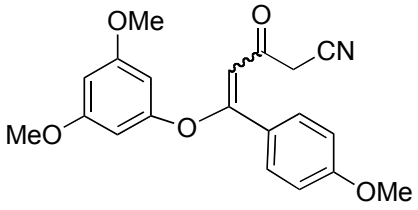
To phosphonate **2.3.6** (134 mg, 0.28 mmol) in THF (5 mL) at 0 ºC under an atmosphere of argon, was added NaH (60% dispersion in mineral oil, 22 mg, 0.56 mmol). The solution was allowed to warm to room temperature over 15 minutes, then freshly distilled benzaldehyde (0.14 mL, 1.4 mmol) was added. The reaction was stirred at room temperature for 20 minutes and then quenched with saturated aqueous NH_4Cl (10 mL). The organic layer was diluted with EtOAc (10 mL) and separated. The organic layer was washed with water (10 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2 10-25% EtOAc in hexane) yielded the title compound as a bright yellow solid (116 mg, 97%). R_f = 0.46 (30% EtOAc in hexanes). Mixture of diastereomers. Mp. 103-106 ºC. IR (thin film) 2959, 2940, 2839, 1638, 1603, 1510 cm^{-1}. ^1H NMR major component (300 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 16 Hz), 7.59 (2H, dd, *J* = 2.0, 8.9 Hz), 7.48-7.31 (5H, m), 7.33 (1H, d, *J* = 14 Hz), 6.88 (2H, dd, *J* = 1.8, 8.0 Hz), 6.44 (1H, s), 6.18 (2H, d, *J* = 2.1 Hz), 6.11 (1H, d, *J* = 2.1 Hz), 3.83 (3H, s), 3.70 (6H, s). ^{13}C NMR major component (75 MHz, $CDCl_3$) δ 188.5, 169.5, 161.6, 161.5, 160.0, 158.4, 135.1, 130.0, 128.8, 128.7, 128.2, 126.9, 126.3, 114.7, 114.3, 95.4, 94.8, 55.5, 55.3. HRMS calculated for $C_{26}H_{24}O_5$ (MH-) 416.1622. Found 416.1624.

5,7-dimethoxy-2-(4-methoxyphenyl)-4-styryl-4*H*-chromen-4-ol (2.3.10)



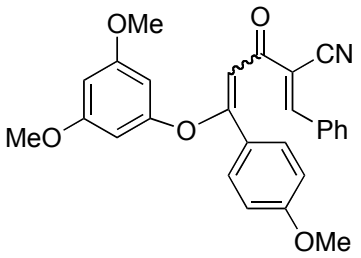
To dienone **2.3.2** (60.0 mg, 0.145 mmol) in dry CH_2Cl_2 (5 mL) at -78 ºC under an atmosphere of argon, was added $TiCl_4$ (0.02 mL, 0.145 mmol). The solution was allowed to warm to room temperature over 1 hour and quenched with the addition of water (7 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (SiO_2, 40% EtOAc in hexane) yielded the title compound as a dark crimson paste (33.1 mg, 55%). R_f = 0.12 (30% EtOAc in hexane). IR (thin film) 3310, 2952, 2936, 2839, 1602, 1511 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 15.8 Hz), 7.44-7.34 (7H, m), 7.02 (1H, s), 6.87 (2H, d, *J* = 8.7 Hz), 6.78 (1H, d, *J* = 16.1 Hz), 6.27 (1H, d, *J* = 2.1 Hz), 6.11 (1H, d, *J* = 2.1 Hz), 6.05 (1H, s), 3.83 (3H, s), 3.80 (3H, s), 3.54 (3H, s). HRMS calculated for $C_{26}H_{25}O_5$ (MH+) 417.1657. Found 417.1654.

5-(3,5-dimethoxyphenoxy)-5-(4-methoxyphenyl)-3-oxopent-4-enenitrile (2.3.15)



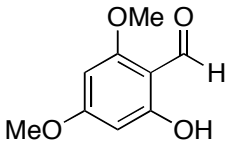
To dry CH_3CN (0.08 mL, 1.45 mmol) in dry THF (1.5 mL) under argon at -78 °C was added *n*-BuLi (2.46 M in hexane, 0.60 mL, 1.45 mmol). Stirred at -78 °C for 1 hour, then ester **2.3.3** (100 mg, 0.29 mmol) in dry THF (1.5 mL) was added dropwise *via* syringe. The solution was stirred for 10 minutes at -78 °C, then quenched with sat. aqueous NH_4Cl (10 mL) and allowed to warm to room temperature. The mixture was extracted with EtOAC (2 x 10mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. Purification by flash column chromatography (SiO_2, 20-30% EtOAc in hexane) yielded the title compound as an yellow oil (37.1 mg, 36%). R_f = 0.20 (30% EtOAc in hexane). IR (thin film) 3006, 2959, 2932, 2839, 2217, 1661, 1602, 1511 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.7 Hz), 6.86 (2H, d, *J* = 8.8 Hz), 6.25 (1H, s), 6.10 (2H, s), 3.86 (2H, s), 3.82 (3H, s), 3.73 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 163.5, 162.3, 161.8, 157.1, 129.3, 124.6, 114.5, 114.4, 112.8, 95.9, 95.4, 55.4, 55.4, 33.0. HRMS calculated for $C_{20}H_{20}NO_5$ (MH+) 354.1345. Found 354.1344.

(2E)-5-(3,5-dimethoxyphenoxy)-2-benzylidene-5-(4-methoxyphenyl)-3-oxopent-4-enenitrile (2.3.16)



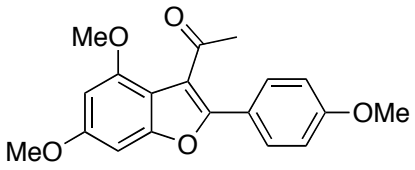
To keto-nitrile **2.3.15** (17.9 mg, 0.05 mmol) in CH_2Cl_2 (0.7 mL) was added benzaldehyde (0.03 mL, 0.26 mmol) and silica gel (12 mg). Stirred at room temperature for 36 hours. The silica gel was then filtered and the solvent removed by rotary evaporation. Purification by flash column chromatography (SiO_2, 10-30% EtOAc in hexane) yielded the title compound as an organish-yellow oil (18.1 mg, 80%). R_f = 0.23 (30% EtOAc in hexane). IR (thin film) 3002, 2955, 2929, 2841, 2206, 1660, 1597, 1571, 1510 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (1H, s), 7.98 (2H, d, *J* = 7.0 Hz), 7.69 (2H, d, *J* = 8.8 Hz), 7.55-7.46 (3H, m), 7.08 (1H, s), 6.91 (2H, d, *J* = 8.8 Hz), 6.17 (2H, s), 3.85 (3H, s), 3.72 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 164.4, 161.4, 158.8, 153.3, 152.4, 133.0, 131.6, 131.1, 129.5, 129.2, 129.1, 114.4, 113.4, 110.7, 106.8, 95.2, 94.9, 55.4, 55.3. HRMS calculated for $C_{27}H_{24}NO_5$ (MH+) 442.1662. Found 442.1662.

2-hydoxy-4,6-dimethoxybenzaldehyde (2.4.9)



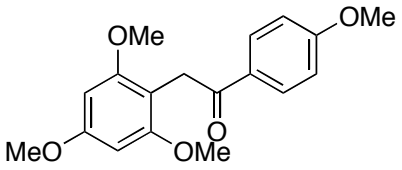
To 2,4,6-trimethoxybenzaldehyde[5] (234 mg, 1.19 mmol) in dry CH_2Cl_2 (3 mL) at 0 ^oC under argon was added BCl_3 (1M in CH_2Cl_2, 1.79 mL, 1.79 mmol). The reaction mixture was warmed to room temperature over 45 minutes, then quenched with 1N HCl (10 mL) and water (10 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the organic fractions dried (Na_2SO_4), filtered and concentrated to yield the title compound as a white solid (216 mg, 100%). R_f = 0.23 (30% EtOAc in hexane). All data was consistent with that reported by De Keukeleire *et. al*.[6]

1-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)ethanone (2.4.1)



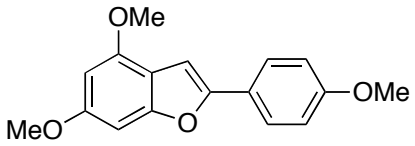
Dry HCl was bubbled through a solution of aldehyde **2.4.9** (993 mg, 5.45 mmol) and 4′-methoxypropiophenone (900 mg, 5.45 mmol) in dry EtOAc (5 mL) for 10 minutes. The flask was capped and allowed to stand at room temperature for 23 hours where a dark crimson solid had precipitated. The solid was filtered and dried under vacuum. The red salt (470 mg, 1.36 mmol) was dissolved in MeOH (5 mL) and 4N HCl (1 mL) and H_2O_2 (30% aqueous, 2.1 g, 13.6 mmol) was added. A solid immediately crashed out of the solution. The reaction was allowed to go for 30 minutes, then the solid was filtered and washed with water to give the title compound as an off-white foam (66.0 mg, 15% from salt). R_f = 0.46 (30% EtOAc in hexane). IR (thin film) 3003, 2964, 2939, 2839, 1689, 1611, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, dd, *J* = 2.0, 8.8 Hz), 6.96 (2H, dd, *J* = 2.0, 8.8 Hz), 6.68 (1H, d, *J* = 2.2 Hz), 6.37 (1H, d, *J* = 2.2 Hz), 3.90 (3H, s), 3.87 (3H, s), 3.85 (3H, s), 2.59 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 160.7, 159.6, 155.3, 153.3, 152.0, 128.6, 122.8, 116.8, 114.0, 110.6, 94.8, 88.4, 55.6, 55.5, 55.2, 32.6. HRMS calculated for $C_{19}H_{19}O_5$ (MH+) 327.1227. Found 327.1229.

2-(2,4,6-trimethoxyphenyl)-1-(4-methoxyphenyl)ethanone (2.4.13)



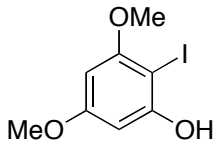
To a mixture of sodium *tert*-butoxide (1.30 g, 13.5 mmol), $Pd(OAc)_2$ (60.0 mg, 0.266 mmol) and tricyclohexylphosphine (74.5 mg, 0.266 mmol) in dry dioxane (23 mL) and under an argon atmosphere was added 2-iodo-1,3,5-trimethoxybenzene (3.91 g, 13.3 mmol) and 4'-methoxyacetophenone (1.99 g, 13.3 mmol). The reaction mixture was heated to 100 ºC for 6.25 hours then cooled to room temperature. The reaction mixture was diluted with Et_2O (100 mL) and the organic layer was washed with water (50 mL). The aqueous layer was extracted with EtOAc (60 mL) and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated *via* rotary evaporation. Recrystallization from 95% EtOH yielded the title compound as an off-white solid (3.40 g, 81%). Mp. 134-135 ºC. R_f = 0.24 (30% EtOAc in hexane). IR (thin film) 2936, 2835, 1684, 1599 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* = 8.8 Hz), 6.92 (2H, d, *J* = 8.8 Hz), 6.15 (2H, s), 4.20 (2H, s), 3.86 (3H, s), 3.81 (3H, s), 3.73 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 163.0, 160.2, 158.8, 130.3, 113.5, 113.4, 104.8, 90.6, 55.6, 55.3, 55.2, 33.2. HRMS calculated for $C_{18}H_{21}O_5$ (MH+) 317.1387. Found 317.1389.

4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran (2.4.2)



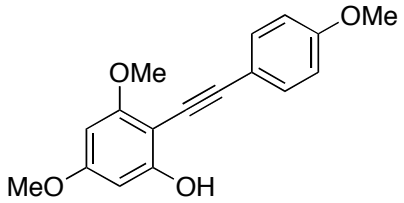
To ketone **2.4.13** (104 mg, 0.33 mmol) in dry CH_2Cl_2 (1.5 mL) at room temperature under an argon atmosphere was added BCl_3 (0.33 mL, 0.33 mmol). The reaction mixture was stirred at room temperature for 5 minutes then poured onto water (10 mL). The layers were separated and aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2, 20% EtOAc in hexane) yielded the title compound as a white crystalline solid (53.2 mg, 52%). Mp. 97-98 ºC. R_f = 0.46 (30% EtOAc in hexane). IR (thin film) 3000, 2937, 2836, 1616, 1506, 1498 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (2H, dd, J = 1.8, 7.1 Hz), 6.96 (2H, dd, J = 1.9, 6.7 Hz), 6.90 (1H, s), 6.69 (1H, d, J = 1.7 Hz), 6.33 (1H, d, J = 1.7 Hz), 3.92 (3H, s), 3.86 (3H, s), 3.85 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 158.8, 156.4, 153.8, 153.3, 125.7, 123.7, 114.2, 113.4, 97.0, 94.3, 88.3, 55.8, 55.6, 55.3. HRMS calculated for $C_{17}H_{16}O_4$ (MH+) 284.1049. Found 284.1045.

2-Iodo-3,5-dimethoxyphenol (2.4.15)



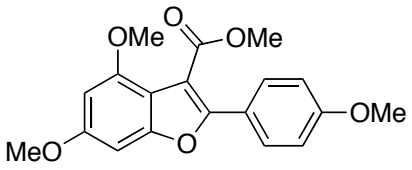
To a suspension of 3,5-dimethoxyphenol (2.57 g, 16.66 mmol) and H_2O_2 (30% solution, 1.23 g, 10.83 mmol) in H_2O (30 mL), was added iodine (2.11 g, 8.33 mmol). The solution was stirred at room temperature for 1 hour until the solution became clear. The aqueous solution was extracted CH_2Cl_2 (60 mL), and washed with 5% aqueous $Na_2S_2O_3$ (30 mL) and H_2O (30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification *via* flash column chromatography (SiO_2 eluting with 10% EtOAc/hexanes) gave iodophenol **2.4.15** as a colorless solid (3.03 g, 65%) R_f = 0.30 (30% EtOAc in hexanes). Mp. 61-64 ºC. IR (thin film) 3462, 3003, 2940, 2840, 1587, 1465 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (1H, d, *J* = 2.9 Hz), 6.07 (1 H, d, *J* = 2.8 Hz), 5.51 (1H, s), 3.85 (3H, s), 3.79 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 158.7, 156.2, 92.7, 91.7. 66.8, 56.1, 55.2. HRMS calculated for $C_8H_{10}O_3I$ (MH+) 280.9675. Found 280.9678. 4-iodo-3,5-dimethoxyphenol was isolated as a tan solid (1.49 g, 32%) R_f = 0.12 (30% EtOAc in hexanes) Mp. 122-123 ºC. IR (thin film) 3413, 1602, 1584, 1559 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ 9.76 (1H, s), 6.11 (2H, s), 3.73 (6H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.0, 159.2, 92.7, 64.0. 46.1. HRMS calculated for $C_8H_{10}O_3I$ (MH+) 280.9675. Found 280.9678.

3,5-dimethoxy-2-(4-methoxyphenylethynyl)phenol (2.4.14)



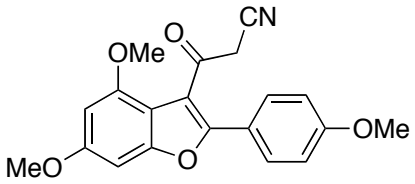
To a stirred solution of 4-methoxyphenylacetylene (1.58 g, 12.01 mmol) and iodophenol **2.4.15** (3.06 g, 10.92 mmol) in anhydrous THF (25 mL) at 0°C under an atmosphere of argon, was added ethylmagnesium bromide (2.5 M solution in ethyl ether, 9.17 mL, 22.93 mmol) drop-wise. After 5 minutes at this temperature, the solution was allowed to warm briefly to room temperature and dichlorobis(triphenylphosphine)palladium(II) (146 mg, 0.21 mmol) was added. The solution was heated at reflux for 2 hours at which time the cloudy yellow solution was quenched with the addition of ice (ca. 15 g). The reaction mixture was diluted with 0.5 M aqueous HCl (40 mL) and extracted with EtOAc (2 x 80 mL). The combined organic extracts were subsequently dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. Purification over SiO_2 eluting with 20% EtOAc/hexanes yielded the title compound as a pale yellow solid (2.55 g, 82%) R_f = 0.33 (30% EtOAc in hexanes). Mp. 86–87 °C . IR (thin film) 3472, 3002, 2963, 2936, 2839, 1620, 1576, 1515, 1457 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, dd, *J* = 1.6, 7.2 Hz), 6.88 (2H, dd, *J* = 2.0, 6.8 Hz), 6.20 (1H, d, *J* = 2.1 Hz), 6.06 (1H, d, *J* = 2.1), 5.99 (1H, s), 3.87 (3H, s), 3.84 (3H, s), 3.81 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 160.9, 159.7, 158.7, 133.1, 115.0, 113.9, 98.9, 92.4, 92.1, 91.4, 78.2, 56.0, 55.5, 55.3. HRMS calculated for $C_{17}H_{17}O_4$ (MH+) 285.1127. Found 285.1126.

4,6-Dimethyl-2-(4-methoxyphenyl)benzofuran-3-carboxylic acid methyl ester (2.4.3)



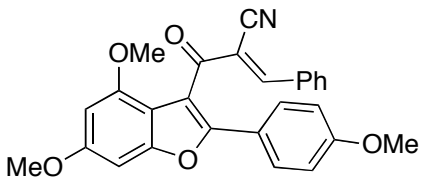
Carbon monoxide (1 atm, balloon pressure) was bubbled through a solution of phenol **2.4.14** (3.01g, 10.58 mmol) in MeOH (60 mL) over a period of 10 min. $Pd(OAc)_2$ (48.0 mg, 0.21 mmol), CBr_4 (7.72 g, 23.28 mmol), and $NaHCO_3$ (1.96 g, 23.28 mmol) were added and the solution stirred vigorously under an atmosphere of carbon monoxide for 20 hours. The solution was diluted with EtOAc (100 mL) and filtered through a silica gel plug. The filtrate was washed with water (20 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The resulting crude oil was chromatographed over SiO_2 eluting with 10–25% EtOAc/hexanes to yield the title compound **2.4.3** as a yellow solid (2.72 g, 75%). R_f = 0.23 (25% EtOAc in hexanes). Mp. 107–108 °C. IR (thin film) 3001, 2951, 2838, 1730, 1623, 1616, 1506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, dd, *J* = 9.0, 1.9 Hz,), 6.96 (2H, dd, *J* = 8.9, 2.1 Hz), 6.66 (1H, d, *J* = 1.8 Hz), 6.36 (1H, d, *J* = 1.8 Hz), 3.92 (3H, s), 3.89 (3H, s), 3.86 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 160.2, 159.4, 155.3, 153.6, 153.4, 128.5, 122.3, 113.9, 110.7, 107.7, 95.1, 87.9, 55.8, 55.7, 55.3, 52.2. HRMS calculated for $C_{19}H_{19}O_6$ (MH+) 343.1182. Found 343.1179.

3-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)-3-oxopropanenitrile (2.4.25)



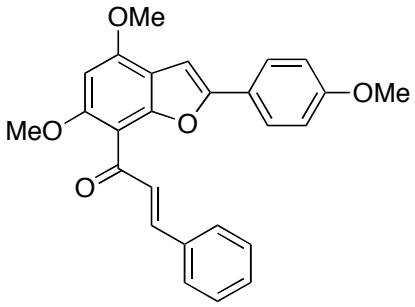
To dry CH_3CN (0.10 mL, 0.28 mmol) in dry THF (0.75 mL) at -78 ºC under argon was added *n*-BuLi (2.46 M in hexanes, 0.11 mL, 0.28 mmol). The mixture was stirred at -78 ºC for 1 hour. Ester **2.4.3** (38 mg, 0.11 mmol) in THF (1.0 mL) was added to the orange solution and the solution was stirred at -78 ºC for 5 minutes. The reaction was quenched with 1N HCl (2 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (2 X 5 mL) and the organic layer was dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2 20-25% EtOAc in hexanes) yielded the title compound **2.4.25** as a yellow solid (19.5 mg, 50 %). R_f = 0.15 (30% EtOAc in hexanes) Mp. 134-136 ºC IR (thin film) 2918, 2839, 2252, 1684, 1609, 1502 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.9 Hz), 6.99 (2H, d, *J* = 8.8 Hz), 6.72 (1H, d, *J* = 1.6 Hz), 6.43 (1H, d, *J* = 1.6 Hz), 4.09 (2H, s), 3.97 (3H, s), 3.88 (3H, s), 3.87 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0, 161.2, 160.0, 155.8, 155.3, 152.8, 129.9, 121.4, 114.4, 114.2, 114.0, 109.3, 95.5, 88.4, 55.9. 55.8, 55.4, 33.7. HRMS calculated for $C_{20}H_{18}NO_5$ (MH+) 352.1180. Found 352.1185.

(E)-1-[4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl]-2-cyano-3-phenylprop-2-en-1-one (2.4.22)



To ketone **2.4.25** (17.1 mg, 0.05 mmol) in EtOH (0.5 mL) at room temperature was added freshly distilled benzaldehyde (0.01 mL, 0.10 mmol) and piperidine (1 drop). Stirred at room temperature for 5 minutes. 1N HCl (2 mL) was added and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2, 10-15% EtOAc in hexane) yielded the title compound as an yellow-orange gum (15.4 mg, 70%). R_f = 0.40 (30% EtOAc in hexane). IR (thin film) 3007, 2957, 2932, 2834, 2218, 1668, 1609, 1504 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.93 (2H, d, *J* = 7.36 Hz), 7.76 (2H, dd, *J* = 2.2, 8.8 Hz), 7.54-7.45 (3H, m), 6.95 (2H, dd, *J* = 2.2, 8.8 Hz), 6.72 (1H, d, *J* = 2.2 Hz), 6.35 (1H, d, *J* = 2.2 Hz), 3.88 (3H, s), 3.84 (3H, s), 3.78 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.2, 169.4, 163.8, 162.1, 160.7, 153.0, 152.6, 133.1, 131.6, 130.5, 128.4, 128.2, 126.8, 125.4, 115.4, 114.4, 108.6, 102.2, 94.5, 93.7, 55.8, 55.4, 55.1. HRMS calculated for $C_{27}H_{22}NO_5$ (MH+) 440.1428. Found 440.1429.

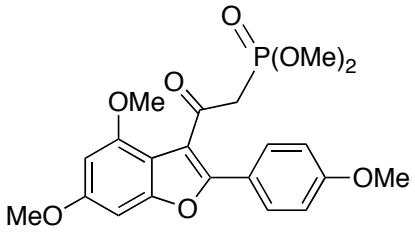
(E)-1-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-7-yl)-3-phenylprop-2-en-1-one (2.4.28)



Titanium(IV) chloride (1.0 M in CH_2Cl_2, 0.28 mL, 0.28 mmol) was added drop-wise to a stirred solution of benzofuran **2.4.2** (53.5 mg, 0.188 mmol) and freshly prepared cinnamoyl chloride (94.0 mg, 0.565 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at room temperature under an atmosphere of argon. The solution was stirred for 10 min, then quenched with the addition of water (3 mL) and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were washed sequentially with water (3 mL), saturated aqueous $NaHCO_3$ (2 x 3 mL), and saturated aqueous NaCl (1 x 3 mL). After drying (Na_2SO_4), the solution was filtered and concentrated by rotary evaporation. Purification by flash column chromatography (SiO_2, 25–50% EtOAc in hexane) furnished the title compound as a yellow solid (38.9 mg, 50%) plus the dienone derived from acylation at the 3-position **2.4.21** (26.2 mg, 33%). Mp. 140–141°C. R_f = 0.12 (30% EtOAc in hexane). IR (thin film) 3001, 2926, 2849, 1653, 1607 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.70 (3H, m), 7.63–7.60 (2H, m), 7.49–7.38 (4H, m), 6.92–6.89 (3H, m), 6.40 (1H, s), 4.03 (3H, s), 3.96 (3H, s), 3.83 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 159.6, 158.1, 155.4, 154.8, 154.3, 142.3, 135.3, 129.9, 128.7, 128.2, 128.0, 125.9, 123.0, 114.1,

108.2, 96.3, 90.7, 57.0, 55.6, 55.2. HRMS calculated for $C_{26}H_{23}O_5$ (MH+) 415.1545. Found 415.1546.

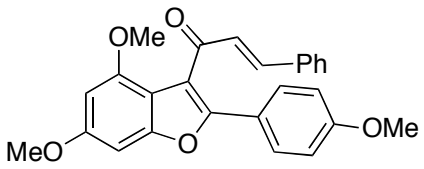
Dimethyl-2-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)-2-oxoethylphosphonate (2.4.29)



To a stirred solution of dimethylmethylphosphonate (0.17 mL, 1.58 mmol) in anhydrous THF (2.0 mL) at –78 °C under an atmosphere of argon was added *n*-butyllithium (2.46 M in hexane, 0.64 mL, 1.58 mmol). After 15 minutes had elapsed, a solution of ester **2.4.3** (135 mg, 0.394 mmol) in anhydrous THF (1 mL, rinsing with an additional 1 mL of THF) was added *via* cannula. The solution was warmed to room temperature over a period of 30 min., then heated at reflux for 1.5 hr. The reaction was quenched with the addition of saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash-column chromatography (SiO_2, eluting with 100% EtOAc) gave the product **2.4.29** as a pale yellow colored solid (152 mg, 89%). Mp. 107–109 °C. R_f = 0.17 (EtOAc). IR (thin film) 3005, 2955, 2847, 1684, 1623, 1610, 1506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (2H, dd, J = 2.1, 6.9 Hz), 6.95 (2H, dd, J = 2.1, 6.9 Hz), 6.69 (1H, d, J = 1.9 Hz), 6.38 (1H, d, J = 2.0 Hz), 3.91 (3H, s), 3.87 (3H, s), 3.86 (3H, s), 3.80 (1H, s), 3.73 (1H, s), 3.60 (3H, s), 3.56 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8 (d, $J_{C,P}$ = 6.15 Hz), 160.6, 159.6, 155.2, 154.0, 153.0, 129.3, 122.1, 116.4, 113.8, 110.2, 95.1, 88.2, 55.8, 55.7, 55.3, 52.7 (d, $J_{C,P}$ = 6.2 Hz), 42.7 (d, $J_{C,P}$ = 129.5 Hz).

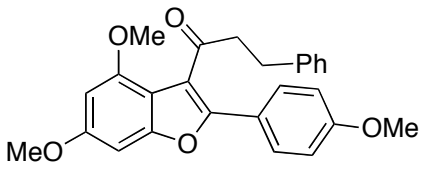
HRMS calculated for $C_{21}H_{24}O_8P$ (MH+) 435.1209. Found 435.1207.

(*E*)-1-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)-3-phenylprop-2-en-1-one (2.4.21)



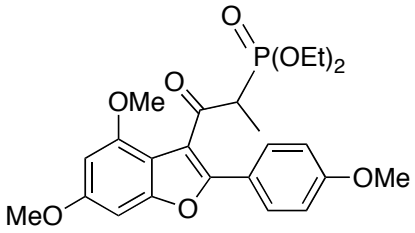
To a stirred solution of phosphonate **2.4.29** (124 mg, 0.286 mmol) in anhydrous THF (2 mL) at 0 °C under an atmosphere of argon, was added sodium hydride (60% in mineral oil, 20.0 mg, 0.5 mmol). The solution was allowed to warm to room temperature, at which time distilled benzaldehyde (0.15 mL, 1.43 mmol) was added. The solution was heated at reflux for 30 minutes, then cooled to room temperature. The intensely yellow solution was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (SiO_2, 10–25% EtOAc in hexane) yielded the dienone **2.4.21** as a viscous yellow wax (0.115 g, 99%). R_f = 0.32 (30% EtOAc in hexane). IR (thin film) 2998, 2955, 2932, 2934, 1643, 1619, 1610, 1502 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, dd, *J* = 2.0, 6.8 Hz), 7.52 (1H, d, *J* = 16.1 Hz), 7.50–7.46 (2H, m), 7.38–7.34 (3H, m), 7.11 (1 H, d, *J* = 16.1 Hz), 6.91 (2H, dd, *J* = 2.1, 6.7 Hz), 6.71 (1H, d, *J* = 2.0 Hz), 6.34 (1H, d, *J* = 1.5 Hz), 3.87 (3H, s), 3.81 (3H, s), 3.78 (3H, s). ^{13}C NMR (75 MHz, CDCl3) δ 192.0, 160.1, 159.6, 155.3, 153.7, 152.4, 144.5, 134.8, 130.4, 128.8, 128.5, 128.4, 127.8, 122.5, 115.2, 114.1, 111.6, 94.9, 88.0, 55.8, 55.7, 55.3. HRMS calculated for $C_{26}H_{23}O_5$ (MH+) 415.1545. Found 415.1536.

1-(4,6-Dimethyl-2-(4-methoxyphenyl)benzofuran-3-yl)-3-phenylpropan-1-one (2.4.34)



Distilled BF_3•OEt_2 (0.05 mL, 0.42 mmol) was added drop-wise to a stirred solution of dienone **2.4.21** (166 mg, 0.40 mmol) and triethylsilane (0.07 mL, 0.42 mmol) in anhydrous CH_2Cl_2 (3.0 mL) at 0 ºC. The deep purple colored solution was allowed to warm to room temperature over a period of 6 hrs. The reaction was quenched with the addition of water (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The title compound was obtained as a pale yellow oil (166 mg, 100 %). R_f = 0.57 (30 % EtOAc in hexane). IR (thin film) 3001, 2934, 2837, 1700, 1695, 1684, 1623, 1616, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.9 Hz), 7.27–7.16 (5H, m), 6.89 (2H, d, *J* = 9.0 Hz), 6.66 (1H, d *J* = 1.5 Hz), 6.34 (1H, d, *J* = 1.8 Hz), 3.86 (3H, s), 3.84 (3H, s), 3.82 (3H, s), 3.22 (2H, t, *J* = 7.5 Hz) 3.04 (2H, t, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 160.2, 159.5, 155.2, 153.3, 151.5, 141.2, 128.5, 128.3, 125.9, 122.4, 116.5, 114.0, 110.9, 94.8, 88.0, 77.2, 55.8, 55.6, 55.3, 46.0, 30.1. HRMS calculated for $C_{26}H_{25}O_5$ (MH+) 417.1702. Found 417.1688.

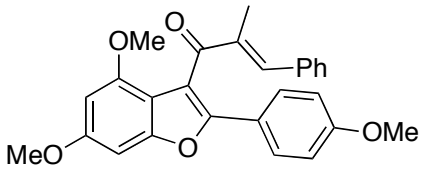
{2-[4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl]-1-methyl-2-oxoethyl}phosphonic acid diethyl ester (2.4.35)



To a stirred solution of distilled diethylethylphosphonate (0.29 mL, 1.77 mmol) in anhydrous THF (6 mL) at –78 °C under argon, was added *n*-butyllithium (2.46M solution in hexane, 0.72 mL, 1.77 mmol). After 20 minutes, ester **2.4.3** (202 mg, 0.59 mmol) in anhydrous THF (2mL, rinsing with 1 mL) was added drop-wise and the solution stirred for one hour at -78 ºC. The reaction was quenched with the addition of saturated aqueous NH_4Cl (10 mL) and the aqueous layer extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed sequentially with water (15 mL) and saturated aqueous NaCl (15 mL), then dried (Na_2SO_4), filtered, and concentrated. Chromatography (SiO_2, EtOAc) yielded the product **2.4.35** as a white crystalline solid (252 mg, 90%). R_f = 0.23 (EtOAc). Mp. 92–93 °C. IR (thin film) 2979, 2940, 2839, 1684, 1623, 1611, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.8 Hz), 6.93 (2H, d, *J* = 8.9 Hz), 6.68 (1H, d, *J* = 2.1 Hz), 6.36 (1H, d, *J* = 1.6 Hz), 4.18 (1H, dq, *J* = 6.9, 25.9 Hz), 3.95–3.62 (4H, m), 3.89 (3H, s), 3.87 (3H, s), 3.85 (3H, s), 1.56 (3H, dd, *J* = 6.5, 14.7 Hz), 1.00 (6H, dt, *J* = 7.1, 64.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6 (d, $J_{C,P}$ = 5.6 Hz), 160.5, 159.4, 155.1, 153.3, 153.0, 129.1, 122.5, 116.7, 113.7, 110.8, 94.9, 88.1, 62.3–62.0 (m), 55.8, 55.7, 55.3, 47.4 (d, $J_{C,P}$ = 126.6 Hz), 16.2 (d, $J_{C,P}$ = 5.4 Hz), 15.8 (d, $J_{C,P}$ = 7.2 Hz),

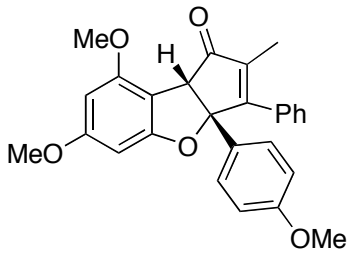
11.2 (d, $J_{C,P}$ = 5.1 Hz). HRMS calculated for $C_{24}H_{30}O_8P$ (MH+) 477.1678. Found 477.1677.

(E)-1-[4,6-Dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl]-2-methyl-3-phenylprop-2-en-1-one (2.4.36)



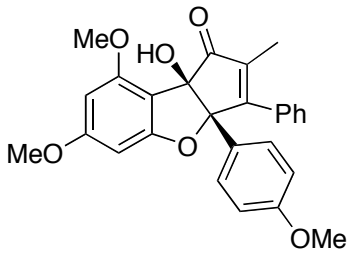
To a solution of phosphonate **2.4.35** (839 mg, 1.76 mmol) and anhydrous lithium chloride (dried at >200°C/0.3mm Hg for thirty minutes; 104 mg, 2.46 mmol) in anhydrous toluene (20 mL) under argon was added freshly distilled DBU (1.05 mL, 7.04 mmol). Freshly distilled benzaldehyde (0.89 mL, 8.81 mmol) was added and the pale yellow solution heated at reflux under argon for 30 hrs. The reaction was cooled to room temperature and saturated aqueous NH_4Cl (30 mL) was added. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with water (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (SiO_2 10–100% EtOAc in hexane) to yield the title compound **2.4.36** (557 mg, 74%) as a yellow colored wax. R_f = 0.37 (30% EtOAc in hexanes). IR (thin film) 3002, 2963, 2928, 2854, 1651, 1622, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, dd, *J* = 2.0, 7.0 Hz), 7.39–7.27 (6H, m), 6.91 (2H, dd, *J* = 2.0, 6.9 Hz), 6.70 (2H, d, *J* = 1.7 Hz), 6.30 (1H, d, *J* = 1.8 Hz), 3.87 (3H, s), 3.82 (3H, s), 3.77 (3H, s), 2.29 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 159.7, 159.4, 154.5, 153.0, 150.0, 141.9, 138.1. 135.2, 129.7, 128.9, 128.5, 127.2, 121.8, 114.5, 113.6, 111.9, 95.0, 88.5, 55.9, 55.8, 55.2, 12.9. HRMS calculated for $C_{27}H_{25}O_5$ (MH+) 429.1702. Found 429.1696.

Cyclopentenone (2.4.38)



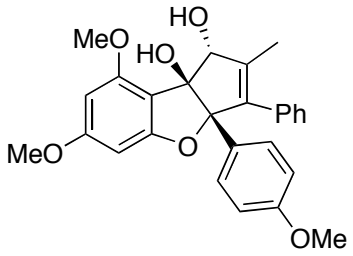
To dienone **2.4.36** (0.38 g, 0.89 mmol) in 1,2-DCE (8.9 mL) under argon was added AcBr (0.10 mL, 1.3 mmol). The solution was heated at 60 ºC for 6 hrs. The solution was cooled to room temperature, and saturated aqueous $NaHCO_3$ (15 mL) was added to neutralize the acid. The aqueous layer was extracted with CH_2Cl_2 (2 X 10 mL). The organic extract was washed with H_2O (5 mL), dried (Na_2SO_4), filtered and concentrated by rotary evaporation. Purificaton by column chromatography (SiO_2, 20-25% EtOAc in hexanes) yielded the title compound as a yellow solid (0.24 g, 64%). R_f = 0.29 (30% EtOAc in hexane) Mp. 112-115 ºC. IR (thin film) 2959, 2924, 2835, 1710, 1616, 1506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 (6H, m), 7.23 (2H, dd, *J* = 2.1, 6.7 Hz), 6.81 (2H, dd, *J* = 1.8, 6.1 Hz), 6.21 (1H, d, *J* = 2.0 Hz), 6.08 (1H, d, *J* = 1.8 Hz), 4.12 (1H, s), 3.86 (3H, s), 3.79 (3H, s), 3.76 (3H, s), 1.97 (3H, s). ^{13}C NMR(75 MHz, $CDCl_3$) δ 203.7, 163.6, 162.6, 160.9, 159.0, 158.0, 139.0, 132.6, 129.8, 129.1, 128.9, 128.1, 126.0, 123.9, 113.9, 103.2, 97.2, 92.2, 88.6, 77.3, 60.4, 55.8, 55.6, 55.3, 10.2. HRMS calculated for $C_{27}H_{25}O_5$ (MH+) 429.1702. Found 429.1698.

Oxidized Cyclopentenone (2.4.39)



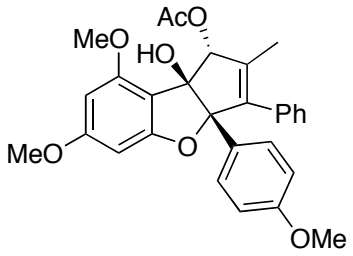
To cyclopentenone **2.4.38** (0.36g, 0.84mmol) in CH_3CN (10 mL) and H_2O (5 mL) at room temperature under argon was added ceric ammonium nitrate (0.97g, 1.77 mmol) in water (5 mL). The solution was stirred at room temperature for 20 minutes when a white powdery solid crashed out. Water (20 mL) was added and the solid was filtered and washed with water (3 x 10 mL) to give the title compound as an off-white solid (0.33 g, 88%). R_f = 0.12 (30% EtOAc in hexane) Mp. 186-189 ºC. IR (thin film) 3442, 2960, 2936, 2838, 1714, 1623 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (5H, s), 7.28 (2H, d, *J* = 8.8 Hz), 6.90 (2H, d, *J* = 8.8 Hz), 6.16 (1H, d, *J* = 2.2 Hz), 6.07 (1H, d, *J* = 1.5 Hz), 3.83 (3H, s), 3.80 (3H, s), 3.78 (3H, s), 2.06 (3H, s). ^{13}C NMR(75 MHz, $CDCl_3$) δ 202.0, 164.0, 160.9, 160.2, 159.5, 158.5, 138.2, 133.1, 129.4, 129.3, 128.3, 127.6, 127.1, 113.8, 99.1, 93.2, 92.5, 88.6, 85.9, 55.7, 55.6, 55.2, 10.5. HRMS calculated for $C_{27}H_{25}O_6$ (MH+) 445.1649. Found 445.1651.

***Trans* diol (2.4.41)**



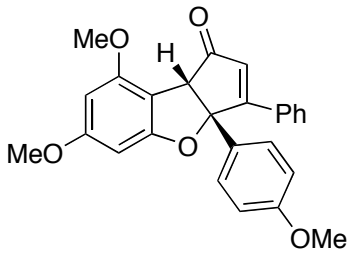
To cyclopentenone **2.4.39** (0.08 g, 0.18mmol) in EtOH (2 mL) at room temperature was added $NaBH_4$ (0.03 g, 0.87 mmol). The solution was stirred at room temperature for 20 minutes then poured onto ice water (5 mL). Saturated ammonium chloride (4 mL) was added and the aqueous layer was extracted with EtOAc (2 X 10 mL). The organic layer was washed with brine (3 mL), dried (Na_2SO_4), filtered and concentrated by rotary evaporation to give the title compound as a white solid (0.08 g, 100%). R_f = 0.25 (50% EtOAc in hexane) Mp. 123-126 ºC. IR (thin film) 3521, 3455, 2964, 2936, 2841, 1611, 1511cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.1 Hz), 7.24-7.15 (5H, m), 6.88 (2H, d, *J* = 8.8 Hz), 6.23 (1H, d, *J* = 2.2 Hz), 6.13 (1H, d, *J* = 1.5 Hz), 5.08 (1H, s), 3.89 (3H, s), 3.80 (3H, s), 3.78 (3H, s), 1.91 (3H, s). ^{13}C NMR(75 MHz, $CDCl_3$) δ 163.8, 159.3, 157.2, 141.8, 136.1, 134.8, 131.6, 129.4, 129.0, 128.2, 127.8, 127.2, 113.9, 107.2, 92.5, 92.1, 89.4, 89.3, 85.8, 55.8, 55.7, 55.2, 12.4. HRMS calculated for $C_{27}H_{27}O_6$ (MH+) 447.1804. Found 447.1808.

***Trans* acetate (2.4.42)**



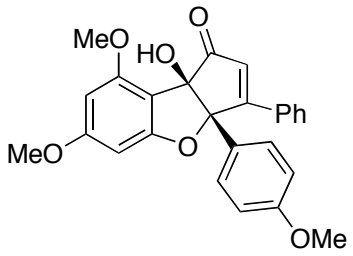
To diol **2.4.41** (49.4 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) under argon at room temperature was added pyridine (0.5 mL), acetic anhydride (0.06 mL, 0.66 mmol) and DMAP (1 crystal). The reaction mixture was stirred at room temperature for 1.5 hours, then poured onto water (3 mL) and extracted with CH_2Cl_2 (5 mL). The organic layer was concentrated by rotary evaporation and dried under vacuum to yield the title compound as a white solid (54.2 mg, 100%) that was used without further purification. Mp. 134-135 ºC. R_f = 0.26 (50% EtOAc in hexane). IR (thin film) 3480, 2956, 2924, 2842, 1739, 1623, 1596, 1513 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 2.2, 8.8 Hz), 7.24-7.18 (5H, m), 6.85 (2H, d, *J* = 2.2, 8.8 Hz), 6.26 (1H, s), 6.20 (1H, d, *J* = 2.2 Hz), 6.06 (1H, d, *J* = 2.2 Hz), 3.79 (3H, s), 3.77 (6H, s), 2.22 (3H, s), 1.80 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 163.6, 161.0, 159.2, 158.3, 139.5, 137.8, 134.5, 129.4, 128.2, 127.9, 127.5, 123.9, 113.6, 104.0, 92.2, 90.7, 88.6, 88.5, 86.6, 55.6, 55.5, 55.1, 21.1, 12.4. HRMS calculated for $C_{29}H_{28}O_7$ (MH+) 488.1835. Found 488.1835.

Cyclopentenone (2.4.31)



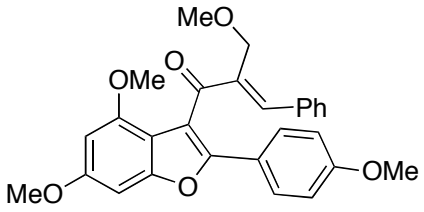
To dienone **2.4.21** (14.0 mg, 0.03 mmol) in dry 1,2-dichloroethane (1 mL) was added (-)-limonene (0.03 mL, 0.17 mmol) and benzoyl bromide (0.02 mL, 0.17 mmol). The reaction mixture was heated to 75 ºC for 30 hrs, then cooled to room temperature. The mixture was poured onto water (3 mL) and diluted with CH_2Cl_2 (3 mL). The layers were separated and the organic layer was washed with sat. aqueous $NaHCO_3$ (2 mL) and brine (2 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated by rotary evaporation. Purification by column chromatography (SiO_2, 20% EtOAc in hexanes) yielded **2.4.31** as a light yellow foam (2.8 mg, 20%) R_f = 0.25 (30% EtOAc in hexanes) IR (thin film) 2961, 2924, 2845, 1710, 1600, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (2H, dd, *J* = 2.2, 8.8 Hz), 7.49-7.30 (5H, m), 6.84 (2H, dd, *J* = 2.2, 8.8 Hz), 6.81 (1H, s), 6.19 (1H, d, *J* = 1.5 Hz), 6.09 (1H, d, *J* = 1.5 Hz), 4.05 (1H, s), 3.85 (3H, s), 3.78 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 168.6, 162.6, 161.2, 159.2, 158.0, 133.7, 132.9, 130.2, 129.5, 128.6, 128.5, 125.8, 114.2, 102.8, 97.4, 92.4, 88.5, 62.5, 55.8, 55.6, 55.2. HRMS calculated for $C_{26}H_{23}O_5$ (MH+) 415.1546. Found 415.1545.

Oxidized Cyclopentenone (2.4.50)



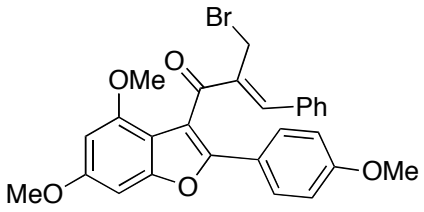
To ketone **2.4.31** (11.2 mg, 0.03 mmol) in MeCN (0.3 mL) and H_20 (0.3 mL) under argon at room temperature was added ceric ammonium nitrate (32.6 mg, 0.06 mmol) in H_20 (0.3 mL). The reaction mixture was stirred at room temperature for 20 min when water (3 mL) was added. The aqueous layer was extracted with EtOAc (3 mL), dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2, 30-40% EtOAc in hexane) yielded the title compound as a light yellow solid (5.2 mg, 40%). R_f = 0.10 (30% EtOAc in hexane). All data was identical to that reported by Taylor.[7]

(E)-1-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)-2-(methoxymethyl)-3-phenylprop-2-en-1-one (2.4.53)



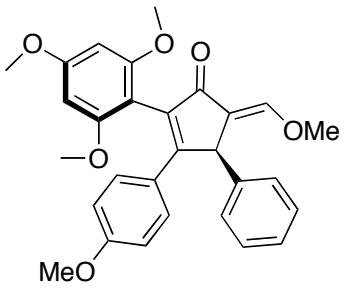
To NaH (436 mg, 60 % dispersion in mineral oil, 10.9 mmol) in dry THF (15 mL) at 0 °C was added MeOH (0.440 mL, 10.9 mmol) dropwise. The solution was warmed to room temperature over 20 minutes. Paraformaldehyde (654 mg, 21.8 mmol) was added to the reaction mixture, followed by dienone **2.4.21** (904 mg, 2.2 mmol) in THF (5 mL). Stirred at room temperature for 22 hours. The reaction mixture was poured onto water (50 mL) and extracted with Et_2O (50 mL). The organic phase was washed with 2N NaOH (2 x 20 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and concentrated. The title compound **2.4.53** was obtained as a yellow wax (1.05 g, 100%). $R_f = 0.46$ (30% EtOAc in hexanes). IR (thin film) 2924, 1652, 1616, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (2H, dd, *J* = 2.0, 8.0 Hz), 7.61 (1H, s), 7.47-7.34 (5H, m), 6.91 (2H, dd, *J* = 2.0, 8.0 Hz), 6.70 (1H, d, *J* = 2.2 Hz), 6.30 (1H, d, *J* = 2.2 Hz), 4.45 (2H, s), 3.87 (3H, s), 3.82 (3H, s), 3.74 (3H, s), 3.52 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 159.9, 159.5, 155.1, 153.5, 148.3, 138.3, 130.1, 129.5, 129.0, 128.5, 128.4, 128.2, 127.9, 127.6, 126.9, 114.1, 94.7, 87.9, 65.1, 58.4, 55.8, 55.5, 55.3. HRMS calculated for $C_{28}H_{27}O_6$ (MH+) 459.1812. Found 459.1808.

(Z)-2-(bromomethyl)-1-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)-3-phenylprop-2-en-1-one (2.4.54)



To dienone **2.4.53** (21.0 mg, 0.05 mmol) in 1,2-DCE (1.0 mL) under argon at room temperature was added cyclohexene (0.01 mL, 0.14 mmol) and acetyl bromide (0.02mL, 0.23 mmol). The reaction mixture was warmed to 45 ºC for 1 hour. The solution was allowed to cool to room temperature, then was diluted with CH_2Cl_2 (3 mL), and washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2 10-20% EtOAc in hexanes) yielded the title compound **2.4.54** as a yellow wax (25.3 mg, 97%). R_f = 0.46 (30% EtOAc in hexanes) IR (thin film) 2932, 2849, 1652, 1615, 1505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* = 8.8 Hz), 7.64-7.38 (6H, m), 6.90 (2H, d, *J* = 8.8 Hz), 6.69 (1H, d, *J* = 2.2 Hz), 6.29 (1H, d, *J* = 2.2 Hz), 4.59 (2H, s), 3.86 (3H, s), 3.81 (3H, s), 3.77 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 168.2, 164.2, 160.1, 159.6, 153.7, 147.1, 137.6, 132.6, 129.8, 128.8, 128.5, 128.3, 128.0, 127.5, 114.1, 100.9, 94.7, 87.8, 55.8, 55.6, 55.3, 29.7. HRMS calculated for $C_{27}H_{23}O_5BrNa$ (MH+) 529.0629. Found 529.06211.

(5*E*)-5-(methoxymethylene)-2-(2,4,6-trimethoxyphenyl)-3-(4-methoxyphenyl)-4-phenylcyclopent-2-enone (2.4.59)



To (-)-limonene (0.140 mL, 0.870 mmol) and acetyl bromide (0.160 mL, 2.20 mmol) in 1,2-dichloroethane (0.5 mL) at room temperature was added dienone **2.4.53** (200 mg, 0.437 mmol) in 1,2-dichloroethane (3.0 mL). The solution was heated to 65 ºC for 6 hours, then cooled to room temperature. Water (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were washed with sat. $NaHCO_3$ (3 mL), dried (Na_2SO_4), filtered and concentrated to give crude **2.4.55** and **2.4.56**.

Brown oil. IR (thin film) 2922, 2843, 1771, 1699, 1652, 1604, 1506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* = 1.5 Hz), 8.08 (1H, d, *J* = 1.5 Hz), 7.45-7.13 (14H, m), 6.64 (2H, dd, *J* = 1.8, 8.8 Hz), 6.63 (2H, dd, *J* = 2.0, 8.8), 6.46 (1H, d, *J* = 2.2 Hz), 6.45 (1H, d, *J* = 2.2 Hz), 6.39 (1H, d, *J* = 2.2 Hz), 6.32 (1H, d, *J* = 2.2 Hz), 5.22 (1H, d, *J* = 1.5 Hz), 5.15 (1H, d, *J* = 1.5 Hz), 3.87 (3H, s), 3.82 (3H, s), 3.73 (3H, s), 3.70 (3H, s), 3.69 (3H, s), 3.40 (3H, s), 2.16 (3H, s), 2.08 (3H, s). LRMS found for $C_{31}H_{29}O_8$ (MH+) 529.

The material was then dissolved in dioxane (10 mL) and 2N NaOH (3 mL) was added. The reaction mixture was stirred at room temperature for 45 minutes and then poured onto 1N HCl (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL),

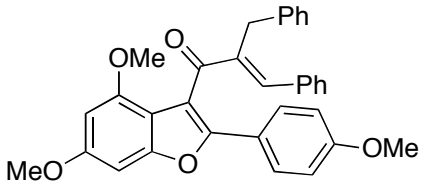
followed by washing the organic extracts with brine (3 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give a mixture of **2.4.57** and **2.4.58**.

Colorless foam. IR (thin film) 3320 (br), 2835, 1683, 1653, 1602, 1506 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.07(14H, m), 6.96 (2H, d, *J* = 9.5 Hz), 6.65 (2H, d, *J* = 9.5 Hz), 6.63 (2H, d, *J* = 8.8 Hz), 6.32 (1H, d, *J* = 3 Hz), 6.22 (1H, d, *J* = 2.2 Hz), 6.12 (1H, d, *J* = 1.5 Hz), 5.95 (1H, d, *J* = 2.2 Hz), 5.08 (1H, s), 4.90 (1H, s), 3.82 (6H, s), 3.70 (3H, s), 3.69 (3H, s), 3.54 (3H, s), 3.12 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 199.7, 165.3, 162.0, 160.5, 158.9, 158.7, 158.6, 158.0, 157.2, 155.6, 141.2, 140.1, 133.3, 130.5, 130.2, 129.9, 129.7, 129.4, 129.1, 128.9, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 127.3, 127.0, 126.8 118.4, 113.6, 113.4, 102.5, 95.9, 94.9, 92.9, 92.5, 60.4, 55.6, 55.3, 55.1, 54.8, 50.2, 29.7, 21.0. HRMS calculated for $C_{27}H_{25}O_6$ (MH+) 445.1640. Found 445.1651.

The crude material was then taken up in CH_3CN (3 mL) and MeOH (0.3 mL). Diisopropylethylamine (0.17 mL, 0.96 mmol) and trimethylsilyldiazomethane (2M in Et_2O, 0.48 mL, 0.96 mmol) were added. The solution was stirred at room temperature for 17 hours. Water (5 mL) was added and the aqueous solution was extracted with EtOAc (2 X 10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2 30-50% EtOAc in hexanes) yielded the title compound **2.4.59** as a yellow solid (46.7 mg, 23%). R_f = 0.11 (50% EtOAc in hexanes) Mp. 182-184 °C IR (thin film) 3427, 2838, 1695, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 7.4 Hz), 7.22 (2H, d, *J* = 8.8 Hz), 7.25-7.12 (4H, m), 6.60 (2H, d, *J* = 8.8 Hz), 6.24 (1H, d, *J* = 2.2 Hz), 6.16 (1H, d, *J* = 2.2 Hz), 5.08 (1H, s), 3.85 (3H,

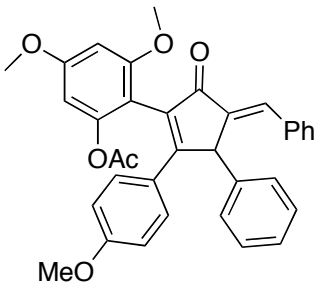
s), 3.78 (3H, s), 3.72 (3H, s), 3.67 (3H, s), 3.56 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 161.8, 161.5, 160.0, 159.1, 158.5, 152.2, 141.5, 135.6, 129.9, 128.2, 127.5, 126.2, 119.9, 113.3, 106.8, 91.5, 91.3, 77.2, 61.6, 55.9, 55.3, 55.0, 49.1, 29.7. HRMS calculated for $C_{29}H_{29}O_6$ (MH+) 473.1957. Found 473.1964.

(E)-2-benzyl-1-(4,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-yl)-3-phenylprop-2-en-1-one (2.4.60)



To ketone **2.4.34** (21.7 mg, 0.05 mmol) in 1,4-dioxane (0.5 mL) was added benzaldehyde (0.01 mL, 0.10 mmol) and concentrated HCl (2 drops). Stirred at room temperature for 3 days. Water (2 mL) was added and the aqueous layer was extracted with EtOAc (2 x 5 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2, 10% EtOAc in hexane) yielded the title compound as a yellow wax (12.6 mg, 50%). R_f = 0.41 (30% EtOAc in hexane). IR (thin film) 3063, 3029, 2933, 1654, 1616, 1496 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (1H, s), 7.54 (2H, dd, *J* = 2.2, 8.8 Hz), 7.30-7.24 (10H, m), 6.82 (2H, dd, *J* = 2.2, 8.8 Hz), 6.69 (1H, d, *J* = 1.5 Hz), 6.29 (1H, d, *J* = 1.5 Hz), 4.13 (2H, s), 3.87 (3H, s), 3.81 (3H, s), 3.68 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 160.1, 159.4, 155.1, 153.5, 150.6, 146.4, 140.8, 140.1, 139.3, 135.3, 129.4, 129.0, 128.8, 128.4, 127.7, 127.5, 126.9, 125.9, 114.0, 94.6, 87.9, 87.8, 55.8, 55.4, 55.2, 31.7. HRMS calculated for $C_{33}H_{29}O_5$ (MH+) 505.2008. Found 505.2015.

2-({4*E*}-4-benzylidene-2-(4-methoxyphenyl-5-oxo-3-phenylcyclopent-1-enyl)-3,5-Dimethoxyphenyl acetate (2.4.63 and 2.4.64)



To dienone **2.4.60** (23.1 mg, 0.046mmol) in 1,2-DCE (1.0 mL) under argon at room temperature was added acetyl bromide (0.02 mL, 0.23 mmol). The reaction mixture was heated to 65 ºC for 4 hours, then cooled to room temperature. Water (3 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by flash column chromatography (SiO_2, 10% EtOAc in hexane) yielded the title compound as a light yellow foam (12.6 mg, 50%). R_f = 0.43 (50% EtOAc in hexane). IR (thin film) 2983, 2925, 2864, 1763, 1683, 1606, 1506 cm^{-1}. ^1H NMR (1:1 mix) (300 MHz, $CDCl_3$) δ 7.59-7.42 (6H, m), 7.35-7.20 (10H, m), 7.18-7.04 (10H, m), 6.69 (2H, dd, *J* = 2.2, 8.8 Hz), 6.68 (2H, dd, *J* = 2.2, 8.8 Hz), 6.45 (1H, d, *J* = 1.5 Hz), 6.42 (1H, d, *J* = 1.5 Hz), 6.34 (1H, d, *J* = 1.5 Hz), 6.30 (1H, d, *J* = 1.5 Hz), 5.41 (1H, s), 5.37 (1H, s), 3.88(3H, s), 3.81 (3H, s), 3.79 (3H, s) 3.75 (3H, s), 3.74 (3H, s), 3.39 (3H, s)2.17 (3H, s), 1.95 (3H, s). HRMS calculated for $C_{35}H_{31}O_6$ (MH-) 546.2036. Found 546.2042.

3.3 References

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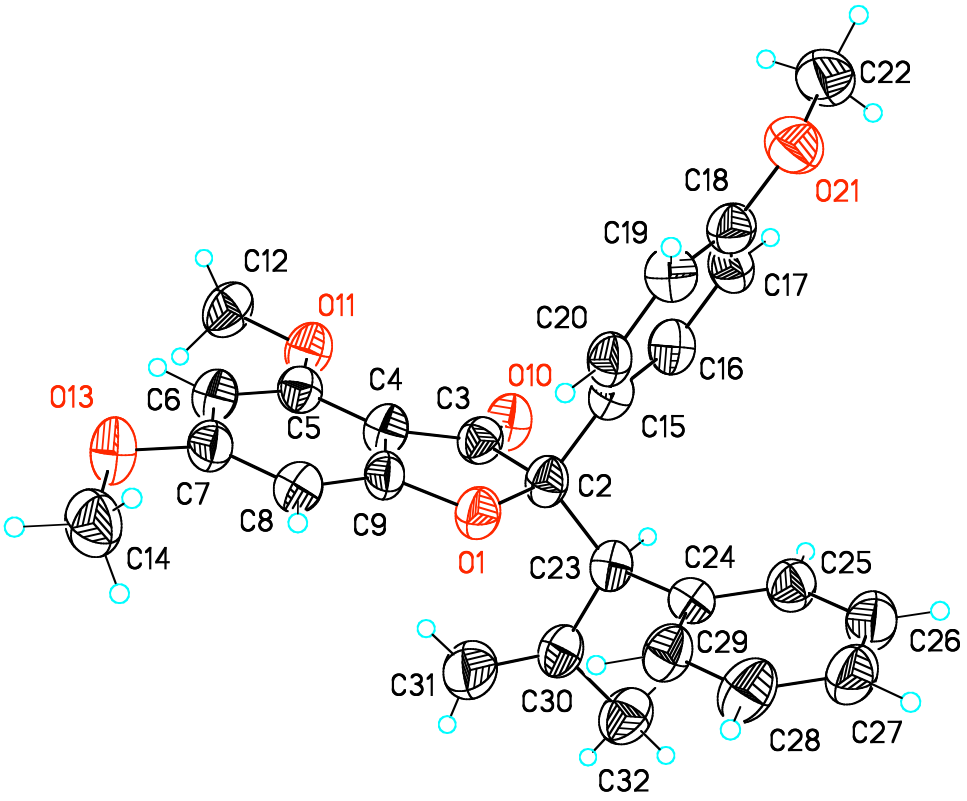
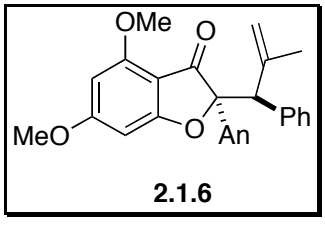
Appendix 1: X-ray Data for Compound 2.1.6





2.1.6

X-ray Experimental for $C_{27}H_{26}O_5$: Crystals grew as long, colorless laths by slow evaporation from ethyl acetate/hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.29 x 0.14 x 0.06 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKa radiation (l = 0.71073Å). A total of 155 frames of data were collected using w-scans with a scan range of 2° and a counting time of 114 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(s(F_o))^2 + (0.044*P)^2]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.175, with R(F) equal to 0.0720 and a goodness of fit, S, = 1.00. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (4.2(18)x10^{-6})* F_c^2 l^3/(sin2q)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond

lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in the supplemental information.

Supplementary Table 1. Crystal data and structure refinement for **2.1.6**.

Empirical formula	C27 H26 O5	
Formula weight	430.48	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.972(2) Å	a= 63.741(8)°.
	b = 10.948(2) Å	b= 64.666(6)°.
	c = 11.812(2) Å	g = 64.291(7)°.
Volume	1096.5(3) $Å^3$	
Z	2	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	456	
Crystal size	0.24 x 0.14 x 0.06 mm	
Theta range for data collection	2.01 to 25.00°.	
Index ranges	-12<=h<=12, -11<=k<=12, -13<=l<=13	
Reflections collected	5870	
Independent reflections	3785 [R(int) = 0.0781]	
Completeness to theta = 25.00°	98.1 %	

Max. and min. transmission	0.9947 and 0.9789
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3785 / 0 / 294
Goodness-of-fit on F^2	0.995
Final R indices [I>2sigma(I)]	R1 = 0.0720, wR2 = 0.1258
R indices (all data)	R1 = 0.2227, wR2 = 0.1752
Extinction coefficient	$4.2(18)x10^{-6}$
Largest diff. peak and hole	0.234 and -0.205 e.$Å^{-3}$

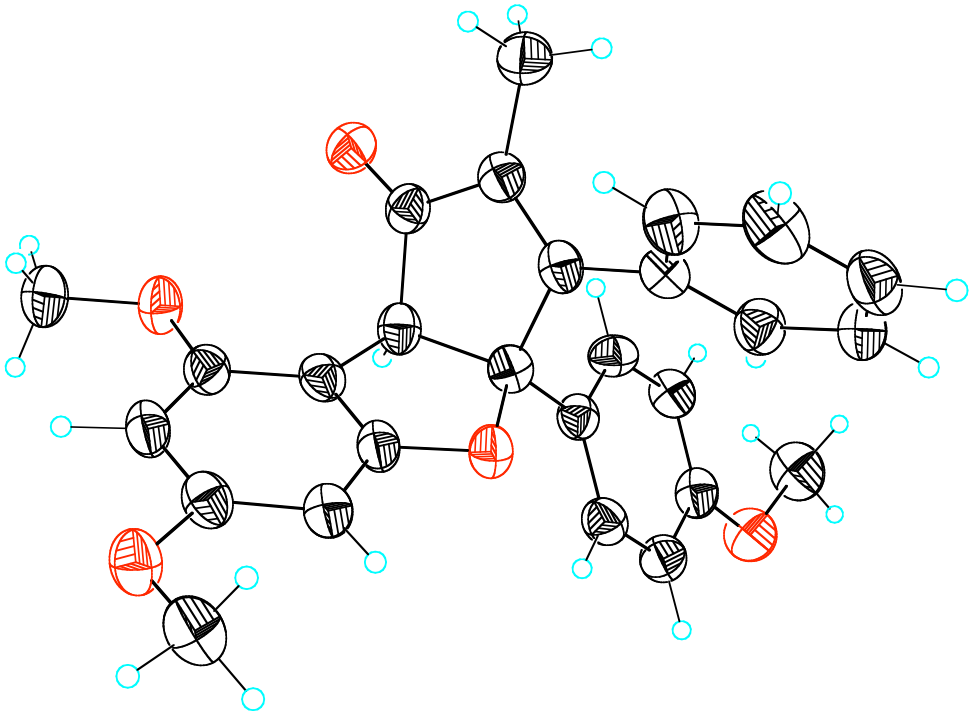
Supplementary Table 2. Atomic coordinates for **2.1.6**

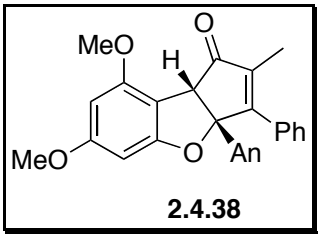
Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.1.6**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	4217(3)	2374(3)	3883(3)	44(1)
C2	2717(5)	2986(5)	4461(4)	42(1)
C3	2142(6)	3948(5)	3257(4)	44(1)
C4	3255(5)	3568(5)	2147(4)	42(1)
C5	3359(5)	3945(5)	813(5)	41(1)
C6	4626(5)	3458(5)	-33(5)	48(1)
C7	5826(5)	2618(5)	417(5)	46(1)
C8	5758(5)	2189(5)	1741(4)	46(1)
C9	4447(5)	2694(5)	2555(4)	40(1)
O10	951(4)	4803(4)	3339(3)	53(1)
O11	2150(3)	4790(3)	474(3)	52(1)
C12	2194(5)	5198(5)	-876(4)	61(2)
O13	7034(4)	2235(3)	-529(3)	59(1)
C14	8355(5)	1620(5)	-217(5)	66(2)
C15	2023(5)	1784(5)	5219(4)	39(1)
C16	575(5)	2084(5)	5752(4)	48(1)
C17	-85(5)	1017(6)	6431(4)	48(1)

C18	732(6)	-380(6)	6569(5)	47(1)
C19	2187(5)	-725(5)	6064(5)	48(1)
C20	2820(5)	358(5)	5388(4)	44(1)
O21	191(4)	-1528(3)	7263(3)	61(1)
C22	-1252(6)	-1262(6)	7402(5)	69(2)
C23	2433(5)	3810(5)	5370(4)	44(1)
C24	2831(5)	2809(5)	6646(5)	41(1)
C25	1788(5)	2670(5)	7851(5)	50(1)
C26	2130(6)	1818(5)	9016(5)	59(2)
C27	3529(6)	1076(5)	8979(5)	58(2)
C28	4569(6)	1194(5)	7791(5)	60(2)
C29	4226(5)	2064(5)	6629(5)	50(1)
C30	3012(5)	5056(5)	4766(5)	49(1)
C31	3887(6)	5402(6)	3611(6)	81(2)
C32	2453(6)	5975(5)	5643(5)	63(2)

Appendix 2: X-ray Data for Compound 2.4.38





2.4.38

X-ray Experimental for $C_{27}H_{24}O_5$: Crystals grew as colorless prisms by slow evaporation from ethyl acetate/hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.25 x 0.12 x 0.04 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKa radiation (l = 0.71073Å). A total of 213 frames of data were collected using w-scans with a scan range of 1.5° and a counting time of 252 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 3. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(s(F_O))^2 + (0.0449*P)^2]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.123, with R(F) equal to 0.0540 and a goodness of fit, S, = 0.992. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_C/[1 + (5.7(11)x10^{-6})* F_C^2 l^3/(sin2q)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed

and calculated structure factors are located in the supplementary information.

Supplementary Table 3. Crystal data and structure refinement for **2.4.38**.

Empirical formula	C27 H24 O5	
Formula weight	428.46	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 12.3190(6) Å	a= 90°.
	b = 10.3129(6) Å	b= 102.139(4)°.
	c = 17.3538(9) Å	g = 90°.
Volume	2155.4(2) $Å^3$	
Z	4	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	904	
Crystal size	0.25 x 0.12 x 0.04 mm	
Theta range for data collection	2.31 to 27.42°.	
Index ranges	-15<=h<=15, -12<=k<=13, -22<=l<=22	
Reflections collected	8721	
Independent reflections	4851 [R(int) = 0.0771]	
Completeness to theta = 27.42°	98.8 %	

Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4851 / 0 / 386
Goodness-of-fit on F^2	0.992
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.0961
R indices (all data)	R1 = 0.1481, wR2 = 0.1227
Extinction coefficient	$5.7(11)x10^{-6}$
Largest diff. peak and hole	0.199 and -0.175 e.$Å^{-3}$

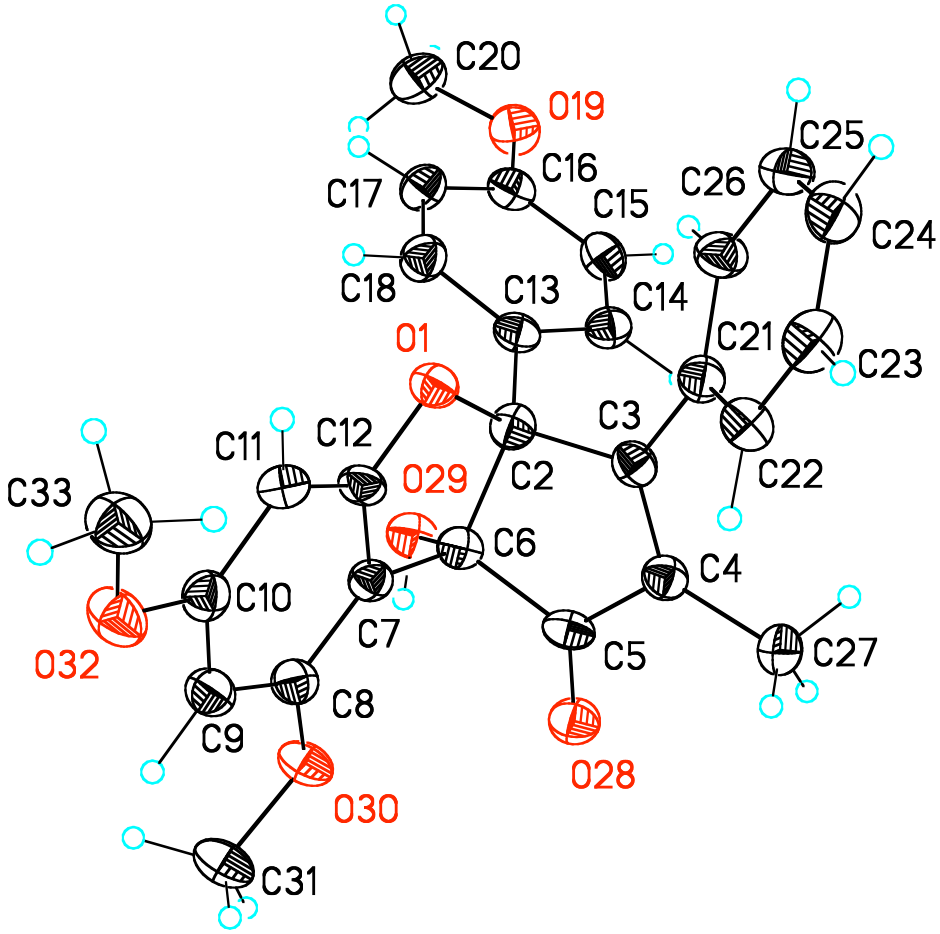
Supplementary Table 4. Atomic coordinates for **2.4.38**

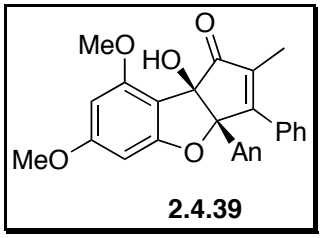
Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.4.38**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	8144(1)	6483(1)	5968(1)	37(1)
C2	7301(2)	7474(2)	5695(1)	34(1)
C3	6573(2)	6996(2)	4920(1)	34(1)
C4	5497(2)	6933(2)	4950(1)	36(1)
C5	5352(2)	7350(2)	5739(1)	36(1)
C6	6489(2)	7466(2)	6276(1)	36(1)
C7	6863(2)	6263(2)	6747(1)	35(1)
C8	6457(2)	5641(2)	7350(1)	37(1)
C9	6980(2)	4539(2)	7694(1)	40(1)
C10	7906(2)	4049(2)	7443(1)	39(1)
C11	8339(2)	4649(2)	6856(1)	37(1)
C12	7787(2)	5751(2)	6533(1)	35(1)
C13	7868(2)	8762(2)	5630(1)	33(1)
C14	7253(2)	9819(2)	5299(1)	39(1)
C15	7739(2)	11001(2)	5201(1)	40(1)
C16	8874(2)	11143(2)	5461(1)	39(1)
C17	9503(2)	10102(2)	5815(1)	41(1)

C18	8997(2)	8921(3)	5885(1)	38(1)
O19	9448(1)	12262(2)	5403(1)	51(1)
C20	8870(3)	13270(3)	4912(2)	59(1)
C21	7075(2)	6599(2)	4252(1)	36(1)
C22	7807(2)	7389(3)	3956(1)	44(1)
C23	8242(2)	6998(3)	3323(1)	50(1)
C24	7984(2)	5799(3)	2987(1)	51(1)
C25	7278(2)	4993(3)	3282(1)	53(1)
C26	6812(2)	5396(3)	3901(1)	48(1)
C27	4517(2)	6588(3)	4317(1)	47(1)
O28	4466(1)	7575(2)	5918(1)	46(1)
O29	5547(1)	6197(2)	7549(1)	44(1)
C30	5129(3)	5572(3)	8161(2)	54(1)
O31	8356(1)	2949(1)	7826(1)	46(1)
C32	9193(3)	2304(3)	7522(2)	49(1)

Appendix 3: X-ray Data for Compound 2.4.39





X-ray Experimental for $C_{27}H_{24}O_6$: Crystals grew as colorless laths by slow evaporation from ethyl acetate/hexanes. The data crystal was cut from a cluster of crystals and had approximate dimensions; 0.25 x 0.09 x 0.05 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKa radiation (l = 0.71073Å). A total of 186 frames of data were collected using w-scans with a scan range of 2° and a counting time of 104 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 5. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms were located in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(s(F_o))^2 + (0.0338*P)^2]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.126, with R(F) equal to 0.0548 and a goodness of fit, S, = 0.957. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (1.5(2)x10^{-5})* F_c^2 l^3/(\sin 2q)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond

lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary information.

Supplementary Table 5. Crystal data and structure refinement for **2.4.39**.

Empirical formula	C27 H24 O6	
Formula weight	444.46	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.2737(5) Å	a= 80.793(2)°.
	b = 10.3745(4) Å	b= 78.723(2)°.
	c = 10.5840(5) Å	g = 85.817(2)°.
Volume	1091.05(9) $Å^3$	
Z	2	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	468	
Crystal size	0.25 x 0.09 x 0.05 mm^3	
Theta range for data collection	1.98 to 27.50°.	
Index ranges	-13<=h<=12, -13<=k<=11, -13<=l<=11	
Reflections collected	7248	
Independent reflections	4900 [R(int) = 0.0539]	
Completeness to theta = 27.50°	97.4 %	

Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4900 / 0 / 395
Goodness-of-fit on F^2	0.957
Final R indices [I>2sigma(I)]	R1 = 0.0548, wR2 = 0.0932
R indices (all data)	R1 = 0.1841, wR2 = 0.1255
Extinction coefficient	$1.45(17)x10^{-5}$
Largest diff. peak and hole	0.236 and -0.259 e.$Å^{-3}$

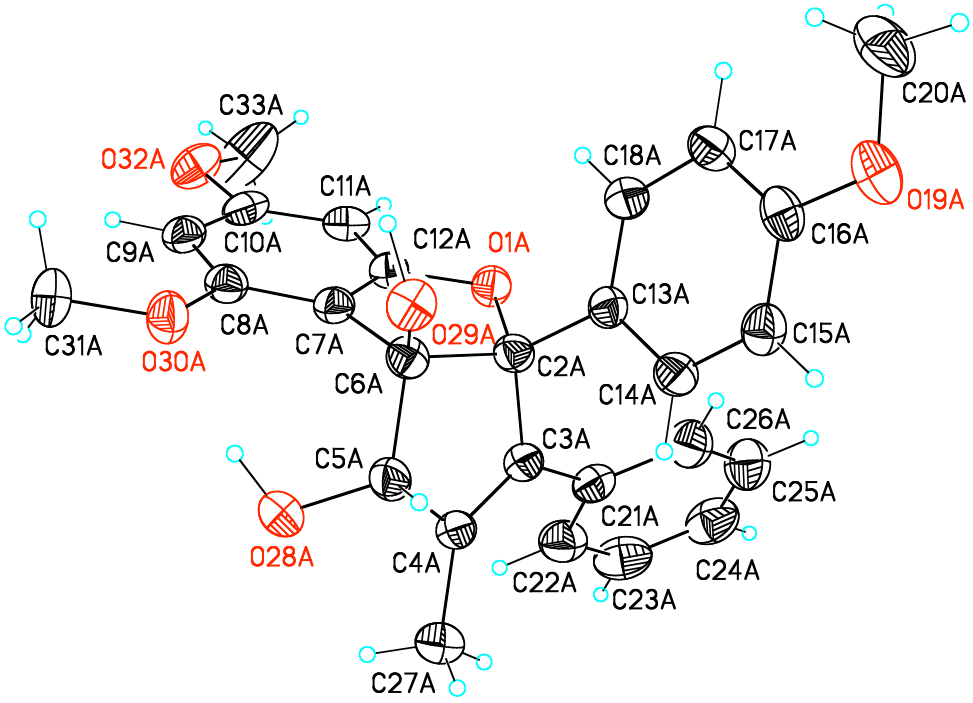
Supplementary Table 6. Atomic coordinates for **2.4.39**

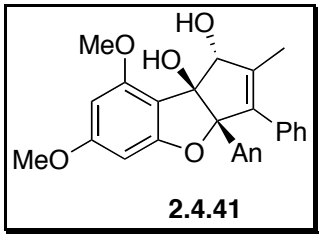
Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.4.39**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	921(2)	5413(2)	3414(2)	27(1)
C2	1751(3)	4338(3)	2902(3)	25(1)
C3	887(3)	3664(2)	2202(3)	25(1)
C4	1444(3)	3600(3)	958(3)	26(1)
C5	2721(3)	4248(3)	635(3)	26(1)
C6	2848(3)	4971(3)	1755(2)	24(1)
C7	2305(3)	6356(3)	1565(3)	23(1)
C8	2739(3)	7439(3)	669(3)	27(1)
C9	2040(3)	8639(3)	723(3)	30(1)
C10	888(3)	8729(3)	1666(3)	27(1)
C11	444(3)	7668(3)	2595(3)	27(1)
C12	1203(3)	6510(3)	2519(3)	25(1)
C13	2312(2)	3507(3)	3988(3)	25(1)
C14	2718(3)	2200(3)	3914(3)	26(1)
C15	3379(3)	1483(3)	4835(3)	31(1)
C16	3641(3)	2059(3)	5844(3)	28(1)
C17	3220(3)	3326(3)	5950(3)	29(1)

C18	2560(3)	4048(3)	5030(3)	31(1)
O19	4356(2)	1277(2)	6680(2)	37(1)
C20	4849(4)	1896(4)	7579(4)	43(1)
C21	-460(3)	3277(3)	2873(3)	27(1)
C22	-1543(3)	3669(3)	2243(3)	31(1)
C23	-2813(3)	3368(3)	2856(3)	35(1)
C24	-3045(3)	2652(3)	4082(3)	38(1)
C25	-2011(3)	2254(3)	4721(3)	36(1)
C26	-718(3)	2582(3)	4123(3)	32(1)
C27	974(4)	2972(4)	-48(3)	35(1)
O28	3546(2)	4231(2)	-363(2)	33(1)
O29	4143(2)	4811(2)	2055(2)	30(1)
O30	3864(2)	7230(2)	-209(2)	33(1)
C31	4432(4)	8331(4)	-1086(3)	40(1)
O32	248(2)	9930(2)	1595(2)	37(1)
C33	-1015(3)	10027(4)	2421(4)	41(1)

Appendix 4: X-ray Data for Compound 2.4.41





2.4.41

X-ray Experimental for $C_{27}H_{26}O_6$: Crystals grew as colorless plates by slow evaporation from ether/hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.10 x 0.10 x 0.04 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKa radiation (l = 0.71073Å). A total of 203 frames of data were collected using w-scans with a scan range of 2° and a counting time of 304 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 7. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atoms on the hydroxyl oxygen atoms were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(s(F_o))^2 + (0.0366*P)^2 + (0.6309*P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_W(F^2)$ refined to 0.131, with R(F) equal to 0.0560 and a goodness of fit, S, = 1.01. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[4] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (2.1(6)x10^{-6})* F_c^2 l^3/(\sin 2q)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables

for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary information.

Supplementary Table 7. Crystal data and structure refinement for **2.4.41**.

Empirical formula	C27 H26 O6	
Formula weight	446.48	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.4937(3) Å	a= 76.264(2)°.
	b = 11.6062(3) Å	b= 73.462(2)°.
	c = 18.1189(6) Å	g = 78.994(2)°.
Volume	2230.95(11) $Å^3$	
Z	4	
Density (calculated)	1.329 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	944	
Crystal size	0.10 x 0.10 x 0.04 mm^3	
Theta range for data collection	2.45 to 27.43°.	
Index ranges	-14<=h<=14, -14<=k<=15, -23<=l<=23	
Reflections collected	16738	
Independent reflections	9995 [R(int) = 0.0460]	
Completeness to theta = 27.43°	98.5 %	

Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9995 / 0 / 613
Goodness-of-fit on F^2	1.007
Final R indices [I>2sigma(I)]	R1 = 0.0560, wR2 = 0.1062
R indices (all data)	R1 = 0.1275, wR2 = 0.1309
Extinction coefficient	$2.1(6)x10^{-6}$
Largest diff. peak and hole	0.246 and -0.228 e.$Å^{-3}$

Supplementary Table 8. Atomic coordinates for **2.4.41**

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.4.41**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

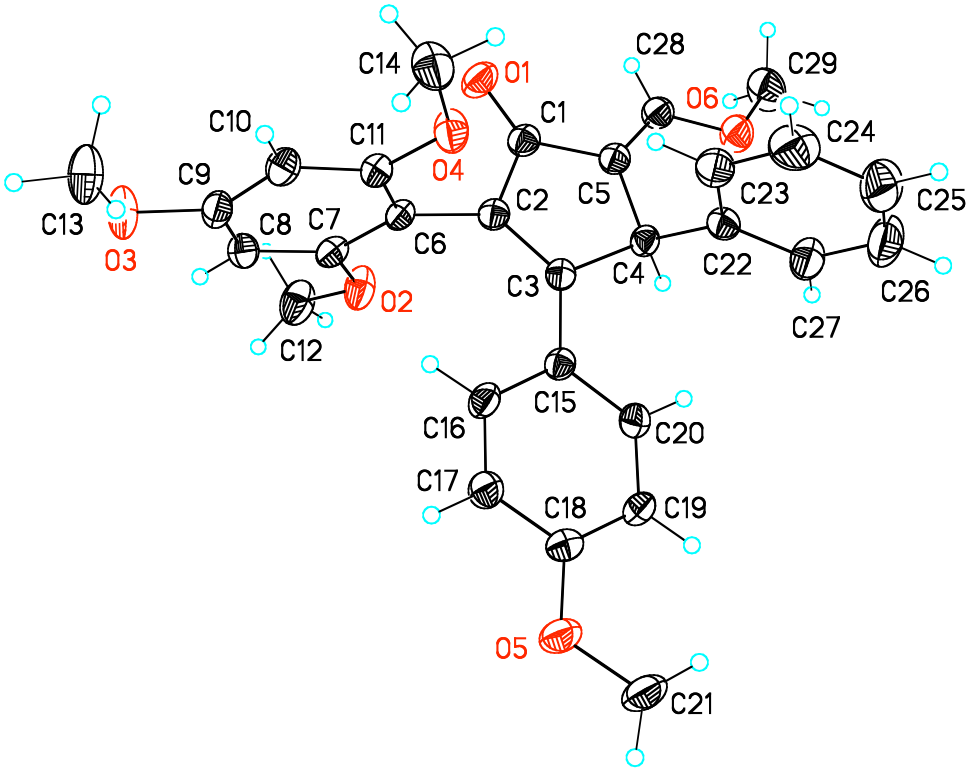
	x	y	z	U(eq)
O1A	1073(1)	337(1)	2744(1)	30(1)
C2A	1165(2)	-3(2)	1998(1)	27(1)
C3A	1061(2)	-1329(2)	2161(1)	28(1)
C4A	2043(2)	-1933(2)	1740(1)	30(1)
C5A	2928(2)	-1109(2)	1201(1)	32(1)
C6A	2544(2)	78(2)	1495(1)	29(1)
C7A	3120(2)	221(2)	2111(1)	27(1)
C8A	4327(2)	326(2)	2078(1)	29(1)
C9A	4612(2)	492(2)	2730(1)	32(1)
C10A	3694(2)	551(2)	3419(1)	32(1)
C11A	2481(2)	496(2)	3469(1)	31(1)
C12A	2238(2)	345(2)	2795(1)	28(1)
C13A	264(2)	854(2)	1595(1)	28(1)
C14A	-166(2)	517(2)	1040(1)	31(1)
C15A	-893(2)	1334(2)	614(1)	33(1)
C16A	-1204(2)	2504(2)	729(1)	33(1)
C17A	-790(2)	2853(2)	1277(1)	36(1)

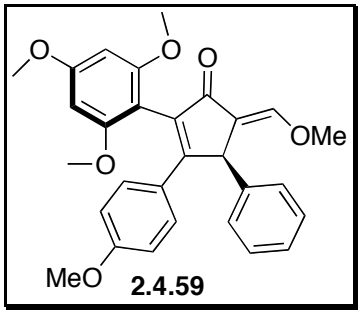
C18A	-58(2)	2020(2)	1701(1)	33(1)
O19A	-1920(1)	3241(2)	274(1)	44(1)
C20A	-2032(2)	4504(2)	258(2)	53(1)
C21A	0(2)	-1838(2)	2753(1)	32(1)
C22A	178(2)	-2918(2)	3275(1)	42(1)
C23A	-800(3)	-3403(3)	3830(2)	50(1)
C24A	-1975(2)	-2829(3)	3885(2)	50(1)
C25A	-2173(2)	-1758(3)	3381(2)	49(1)
C26A	-1199(2)	-1266(2)	2825(1)	41(1)
C27A	2329(2)	-3227(2)	1698(2)	42(1)
O28A	4148(1)	-1641(2)	1196(1)	43(1)
O29A	2701(1)	1015(2)	819(1)	35(1)
O30A	5169(1)	253(2)	1373(1)	37(1)
C31A	6419(2)	333(3)	1326(2)	45(1)
O32A	4104(1)	690(2)	4035(1)	41(1)
C33A	3276(3)	543(3)	4795(2)	73(1)
O1	6170(1)	3717(1)	2323(1)	26(1)
C2	5921(2)	4106(2)	3070(1)	24(1)
C3	5927(2)	5444(2)	2899(1)	25(1)
C4	4901(2)	6010(2)	3297(1)	28(1)
C5	4050(2)	5134(2)	3816(1)	29(1)
C6	4534(2)	3969(2)	3506(1)	25(1)

C7	4082(2)	3824(2)	2831(1)	24(1)
C8	2927(2)	3695(2)	2774(1)	26(1)
C9	2783(2)	3494(2)	2086(1)	27(1)
C10	3804(2)	3405(2)	1451(1)	26(1)
C11	4974(2)	3493(2)	1486(1)	26(1)
C12	5058(2)	3687(2)	2194(1)	23(1)
C13	6826(2)	3363(2)	3514(1)	23(1)
C14	6986(2)	3719(2)	4156(1)	29(1)
C15	7783(2)	3040(2)	4592(1)	29(1)
C16	8445(2)	1996(2)	4381(1)	27(1)
C17	8305(2)	1628(2)	3739(1)	31(1)
C18	7491(2)	2300(2)	3320(1)	28(1)
O19	9270(1)	1256(2)	4760(1)	38(1)
C20	9469(2)	1623(2)	5408(1)	42(1)
C21	6962(2)	5984(2)	2296(1)	28(1)
C22	6722(2)	6874(2)	1672(1)	38(1)
C23	7670(2)	7350(2)	1083(1)	46(1)
C24	8868(2)	6940(3)	1108(2)	51(1)
C25	9119(2)	6054(3)	1718(2)	50(1)
C26	8175(2)	5579(2)	2307(1)	37(1)
C27	4568(2)	7313(2)	3311(2)	41(1)
O28	2806(1)	5605(2)	3825(1)	42(1)

O29	4337(1)	3010(2)	4160(1)	33(1)
O30	1980(1)	3778(1)	3432(1)	33(1)
C31	793(2)	3603(2)	3405(1)	39(1)
O32	3554(1)	3203(1)	798(1)	32(1)
C33	4554(2)	3119(2)	122(1)	40(1)

Appendix 5: X-ray Data for Compound 2.4.59





2.4.59

X-ray Experimental for $C_{29}H_{28}O_6$: Crystals grew as pale yellow prisms by slow evaporation from ethyl acetate/hexanes. The data crystal was cut from a larger crystal and had approximate dimensions; 0.22 x 0.20 x 0.16 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKa radiation (l = 0.71073Å). A total of 252 frames of data were collected using w-scans with a scan range of 2° and a counting time of 66 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 9. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR97[2] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(s(F_O))^2 + (0.0353*P)^2 + (0.5662*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.112, with R(F) equal to 0.0489 and a goodness of fit, S, = 1.01. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and

thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary information.

Supplementary Table 9. Crystal data and structure refinement for **2.4.59**

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Empirical formula	C29 H28 O6	
Formula weight	472.51	
Temperature	153(2) K	
Wavelength	0.71070 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.9524(5) Å	a= 115.559(2)°.
	b = 11.6166(4) Å	b= 100.884(2)°.
	c = 11.8930(7) Å	g = 104.400(3)°.
Volume	1243.94(10) $Å^3$	
Z	2	
Density (calculated)	1.262 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	500	
Crystal size	0.22 x 0.20 x 0.16 mm	
Theta range for data collection	2.04 to 27.50°.	
Index ranges	-12<=h<=14, -14<=k<=15, -15<=l<=15	
Reflections collected	9110	
Independent reflections	5646 [R(int) = 0.0201]	

Completeness to theta = 27.50°	98.8 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5646 / 0 / 321
Goodness-of-fit on F^2	1.014
Final R indices [I>2sigma(I)]	R1 = 0.0489, wR2 = 0.0986
R indices (all data)	R1 = 0.0795, wR2 = 0.1120
Largest diff. peak and hole	0.294 and -0.210 e.$Å^{-3}$

Supplementary Table 10. Atomic coordinates for **2.4.59**

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.4.59**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	4851(1)	125(1)	8197(1)	35(1)
O2	2779(1)	1864(1)	9930(1)	36(1)
O3	-1419(1)	-1624(1)	6822(1)	38(1)
O4	2297(1)	-145(1)	5452(1)	33(1)
O5	1808(1)	6603(1)	8053(1)	37(1)
O6	8540(1)	3255(1)	9077(1)	34(1)
C1	4973(2)	1202(2)	8197(2)	25(1)
C2	3881(2)	1712(2)	7987(1)	22(1)
C3	4389(2)	2975(2)	8125(1)	21(1)
C4	5891(2)	3407(2)	8344(2)	23(1)
C5	6216(2)	2270(2)	8457(2)	24(1)
C6	2480(2)	847(2)	7674(2)	23(1)
C7	1937(2)	910(2)	8658(2)	25(1)
C8	634(2)	76(2)	8351(2)	27(1)
C9	-141(2)	-861(2)	7028(2)	27(1)
C10	373(2)	-986(2)	6018(2)	27(1)

C11	1687(2)	-126(2)	6359(2)	25(1)
C12	2431(2)	1733(2)	10978(2)	41(1)
C13	-2303(2)	-2534(2)	5481(2)	43(1)
C14	1643(2)	-1241(2)	4113(2)	39(1)
C15	3708(2)	3908(2)	8098(1)	22(1)
C16	2315(2)	3554(2)	7799(2)	27(1)
C17	1721(2)	4469(2)	7790(2)	30(1)
C18	2488(2)	5775(2)	8085(2)	27(1)
C19	3865(2)	6164(2)	8406(2)	28(1)
C20	4450(2)	5238(2)	8414(2)	27(1)
C21	2575(2)	7931(2)	8279(2)	40(1)
C22	6235(2)	3548(2)	7212(2)	25(1)
C23	5587(2)	2490(2)	5903(2)	33(1)
C24	5947(2)	2616(2)	4891(2)	47(1)
C25	6954(2)	3796(2)	5178(2)	55(1)
C26	7603(2)	4844(2)	6466(2)	51(1)
C27	7239(2)	4721(2)	7475(2)	36(1)
C28	7422(2)	2228(2)	8804(2)	27(1)
C29	9778(2)	3188(2)	9646(2)	45(1)

Appendices References

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